HetAr–X(M) + R–M(X)

III.2.7 Heteroaromatics via Palladium-Catalyzed Cross-Coupling

KJELL UNDHEIM

A. INTRODUCTION

Heterocyclic aromatic chemistry is a large and important part of organic Chemistry. A great number of reports deal with transition-metal-catalyzed cross-coupling reactions in heteroarenes. A review from 1991 deals with carbon–carbon bond-forming reactions using nickel and palladium catalysis in heterocycles.[1] A comprehensive review over transition metal catalysis in cross-coupling reactions in π-deficient heteroarenes covered the literature up to 1995.[2] Coupling reactions in pyrimidines and benzopyrimidines were summarized in 1996.[3]* This work deals with Pd-catalyzed coupling reactions in the five- and six-membered heteroaromatic ring systems. Other heterocyclic systems assigned aromatic character are normally charged and unstable. Any works with such peripheral structures are not included.

Substrates for cross-coupling of simple heteroaromatics are either commercially accessible or are in most cases readily prepared. Before reviewing cross-coupling reactions, a brief summary of the characteristics of heteroaromatic systems and substitution modes may be useful.

The heteroarenes can broadly be divided into three major groups for the purpose of rationalizing the substitution behavior and characteristics of these systems.

1. The π-excessive heteroaromatics are five-membered rings containing one heteroatom.
2. The π-deficient heteroaromatics, the azines, are six-membered ring systems containing one or more nitrogen atoms.
3. The third group, the azoles, are five-membered ring systems containing one or more heteroatoms in addition to a nitrogen heteroatom.

In the main, the reactivity patterns for groups (1) and (2) can readily be rationalized, whereas the characteristics of azoles can be regarded as arising from a combination of the

*A book on palladium in heterocyclic chemistry has been published very recently. See J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Oxford, 2000.

Handbook of Organopalladium Chemistry for Organic Synthesis, Edited by Ei-ichi Negishi
ISBN 0-471-31506-0

properties of the first two groups. In addition, the nature of the heteroatoms and their relative positions in the azole will affect the properties. Benzannulation in either series leads to slight changes of character, but the principal characteristics of the systems are retained although the relative preference for regiosubstitution may be affected. The annulated systems may perhaps be compared to naphthalene, but the preference for reaction in the benzene or the heterocyclic ring will largely be controlled by the π-excessive or π-deficient nature of the annulated heterocycle. Not unexpectedly, the presence of strongly electron-affecting substituents in the ring may override the usual characteristics of a heterocyclic system.

In the π-excessive systems, an iodo, bromo, or triflyloxy substituent in either position in the substrate is appropriate for cross-coupling reactions. Other useful leaving groups such as phosphoroxy groups have received little attention. Sometimes an α-chloro substituent next to the ring heteroatom can be substituted, but normally coupling at the chloro carbon occurs less readily. The halogen substituents can be introduced into the π-excessive heterocycle by electrophilic substitutions; initial electrophilic substitution is in a vacant α-position to the heteroatom, then in β-positions. Alternatively, halogenation is effected via a metallated species. Metallation generally, and lithiation in particular, takes place in an α-position to the heteroatom using either a lithium amide or an alkyllithium reagent for the H–Li exchange. Halogen–metal exchange can be effected in either positions. Activated metals will insert directly into a carbon–halogen bond. More frequently, the desired metallation is via a metal–metal exchange with the lithiated species in the usual manner. In the annulated systems the carbocycle has largely retained the benzenoid properties.

In the π-deficient systems, metallation is generally more difficult to effect except by halogen–metal exchange in the benzenoid positions, for example, the 3,5-positions in pyridine or the 5-position in pyrimidine. Competitive reactions are frequently observed between lithium–hydrogen or lithium–halogen exchange and nucleophilic addition of the organometallic reagent to the electrophilic positions in these systems. In azines, the α-positions are electrophilic sites, for example, the 2,4,6-positions in pyridine and pyrimidine. The electrophilic character increases with the number of heteroatoms in the ring and varies with the relative locations of the heteroatoms. In most cases a chlorine substituent will be exchanged equally readily as a bromine or iodine substituent in cross-coupling reactions involving electrophilic positions. Relative reactivity, however, may allow for regioselective substitutions. The reactivity is comparable to that of chlorobenzenes substituted by strongly electron-withdrawing groups, or somewhat less reactive than an acid chloride. In most cases, therefore, there is no need for an exchange of a chloro substituent with a bromo or iodo substituent in the electrophilic positions unless it is desirable to change the order of selectivity. Readily available heterocycles often carry hydroxy groups in electrophilic positions and are easily converted into chloro derivatives using simple, common methodology. Bromo or iodo derivatives are less readily available and are most often prepared by a halogen–halogen exchange reaction from the chloro derivatives. Triflates of hydroxy groups in all positions can be prepared.

In the azoles, the coupling characteristics very much follow the pattern from the π-excessive systems. Normally bromo, iodo, or triflyloxy groups are displaced in any position. The halogens are introduced by electrophilic substitutions along the lines outlined for the π-excessive systems, but the regiochemistry depends among other things on the relative position of the annular heteroatoms. Hydroxy groups are replaced by a chlorine substituent in electrophilic positions as in the π-deficient series. Metallated species are commonly

prepared by hydrogen–metal exchange reactions, commonly by lithiation. The lithiated species may subsequently be subjected to a metal–metal exchange operation. The preferential regiochemistry pattern from metallation in the π-excessive systems may be overcome by initial metallation between two heteroatoms in a 1,3-relationship.

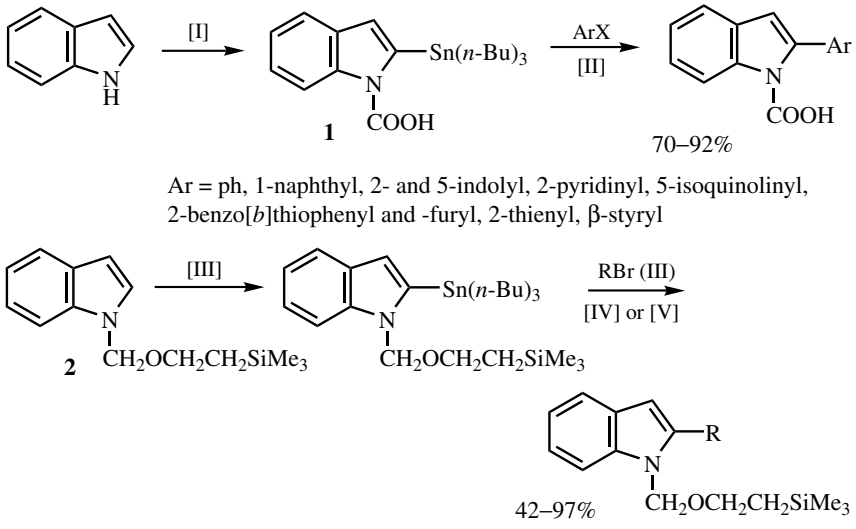
B. CROSS-COUPLING IN π-EXCESSIVE RING SYSTEMS

B.i. Metallated Five-Membered Ring Systems

B.i.a. *Arylation*

Tin Derivatives. α-Metallation followed by electrophilic trapping has become a powerful method in regioselective functionalization of five-membered heteroaromatics. The Stille organotin methodology will provide 2-indolyl-stannanes intermediates for the synthesis of 2-substituted indoles (**Scheme 1**). *N*-Metallation of indole and *N*-carboxylation before a subsequent lithiation and metal–metal exchange can be used for stannylation in the 2-position. The stannane reagent **1** can be prepared on a multigram scale and has been stored for one month at −20 °C.[4] More common protecting groups are often used. An example is provided by the protection of indole with the trimethylsilylethoxymethyl group. The resultant indole derivative **2** undergoes Stille-type couplings with an aryl, a heteroaryl, or vinyl bromides or iodides.[5]

A bromo or triflyloxy substituent in the β-position of the indole can be replaced by stannylation after initial lithiation (**Scheme 2**) . The *N*1-silyl-protected 3-bromo-7-azain-

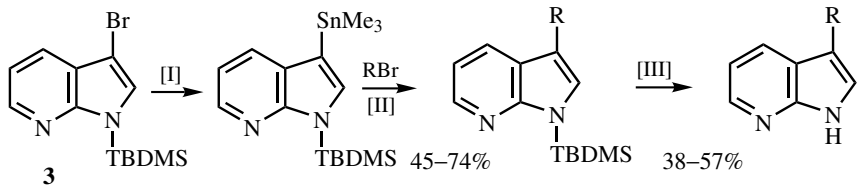


[I] (i) *n*-BuLi, THF, −68 °C, CO_2, (ii) *t*-BuLi, (iii) $(n\text{-Bu})_3SnCl$; [II] 5 mol % $Cl_2Pd(PPh_3)_2$, EtOH, rfx, 24–48 h; [III] (i) *n*-BuLi, THF, −10 °C, (ii) $(n\text{-Bu})_3SnCl$, THF, −20 °C; [IV] 10 mol % $Pd(PPh_3)_4$, DMF, 110 °C, 1–72 h; [V] 5 mol % $Pd_2(dba)_3$, $P(2\text{-furyl})_3$, THF, 60 °C, 2–76 h.

Scheme 1

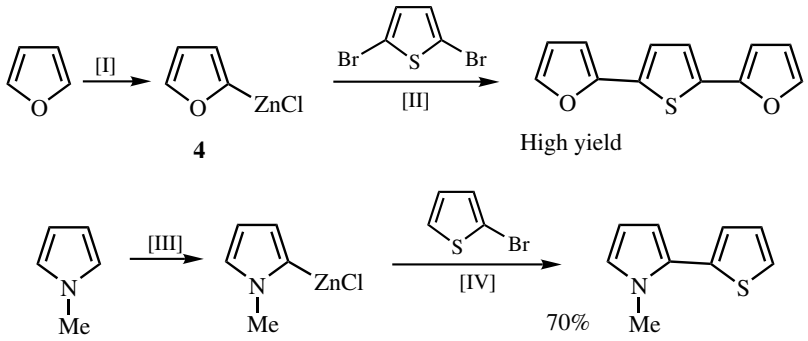
dole **3** was lithiated and converted to the corresponding 3-stannane with trimethylstannyl chloride for coupling with aryl and heteroaryl bromides.[6]

Zinc Derivatives. Furan and *N*-methylpyrrole are lithiated in an α-position (**Scheme 3**). Subsequent zincation by treatment with anhydrous zinc chloride or bromide gives the substrates **4** and **5** for mono- or dicoupling with thiophenes under Negishi conditions.[7]



[I] (i) *t*-BuLi, THF, –90 °C, (ii) Me_3SnCl; [II] 20 mol % $Pd(PPh_3)_4$, LiCl, THF, rfx, 48 h; [III] 10% aq. HCl, r.t.

Scheme 2



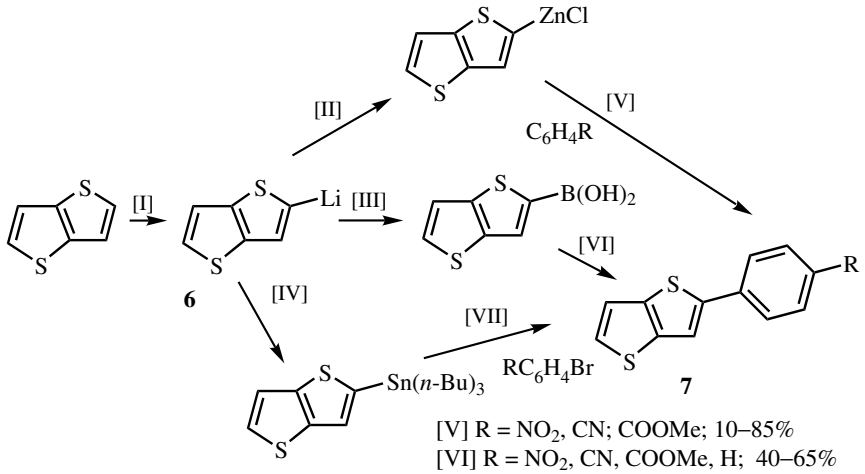
[I] (i) *n*-BuLi, THF, 0 to r.t., (ii) $ZnCl_2$, –40 to r.t. [II] 3 mol % $Cl_2Pd(dppb)$, THF, rfx, 2 h; [III] (i) *n*-BuLi, hexane, TMEDA, rfx, 20 min, (ii) $ZnCl_2$, THF, r.t.; [IV] 3 mol % $Cl_2Pd(dppb)$, THF, rfx, 6 h.

Scheme 3

In a comparative study (**Scheme 4**) of different methods for the preparation of 2-arylthieno[3,2-*b*]thiophenes **7**, the lithiated species **6** was treated with zinc chloride to effect zincation, tributyl borate to effect boronation, and tri(*n*-butyl)stannyl chloride to effect stannylation. Aryl bromides or iodides were used. The yields of the 2-aryl product **7** depend on the substituents in the benzene ring, the metallated species, and the palladium catalyst.[8]

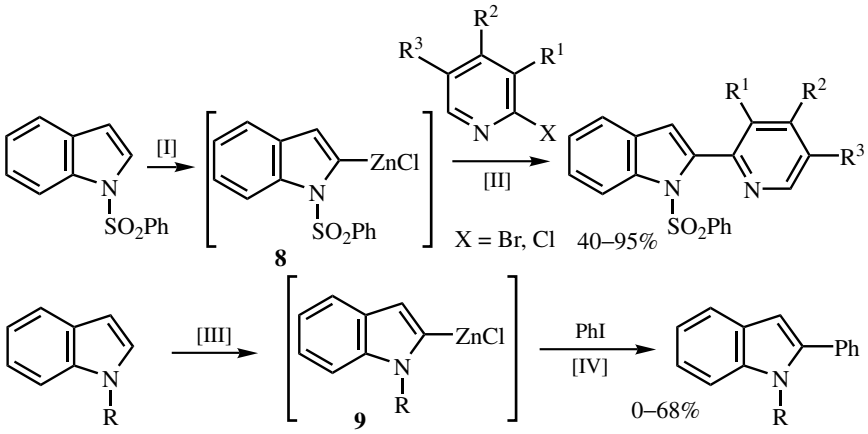
1-(Benzenesulfonyl)-2-indolylzinc chloride **8**, prepared by metathesis of 1-(benzenesulfonyl)-2-lithioindole with $ZnCl_2$, will couple with 2-halogenopyridines to give 2-(2-pyridinyl)indoles (**Scheme 5**). A number of substituted 2-chloro- or 2-bromopyridines were reacted. In the electrophilic pyridine 2-position, the chloro- and bromopyridines react equally well with formation of coupling products. Homocoupled indole was a minor product. Pyrazine as the electrophilic partner with a chloro substituent in the electrophilic

2-position also reacts well. π-Excessive heterocycles used as electrophiles under these conditions give low or moderate yields.[9] In the zincated indole **9** a variety of protecting groups were present in the substrates for the coupling with phenyl iodide.[10]



[I] *n*-BuLi, THF, 0 °C to r.t., 1 h; [II] $ZnCl_2$, 0 °C, 30 min; [III] (i)B[O(*M*-Bu)]$_3$,(ii) aq. NaOH; [IV] $(n\text{-}Bu)_3SnCl$, THF, r.t., 1 h; [V] 2 mol % $Pd(dba)_2$ or 4 mol % PPh_3, DMF, 80 °C, 1 h; [VI] 5 mol % $Pd(PPh_3)_4$, $Ba(OH)_2$, DME, H_2O, rfx, 16–24 h; [VII] 10 mol % $Pd(PPh_3)_4$, dioxane, rfx, 18–36 h.

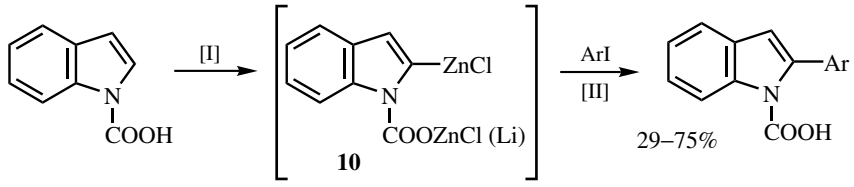
Scheme 4



[I] (i) LDA, THF, 0 °C, (ii) $ZnCl_2$, THF, 25 °C; [II] 2 mol % $Cl_2Pd(PPh_3)_2$, DIBAH, THF, rfx, 4 h; [III] (i) *n*-BuLi, THF, −78 °C, (ii) $ZnCl_2$, THF, −78 °C to r.t.; [IV] 5 mol % $Pd(PPh_3)_4$, THF, rfx, 14–18 h.

Scheme 5

Carbamate protection can also be used in zincation in the indole 2-position for the subsequent coupling (**Scheme 6**). The 1-lithio-oxycarbonyl group also serves as a directing group for vicinal lithiation. Subsequent transmetallation with zinc chloride gives the corresponding lithio-oxycarbonylindolylzinc chloride **10** for coupling with aryl bromides or iodides.[10]

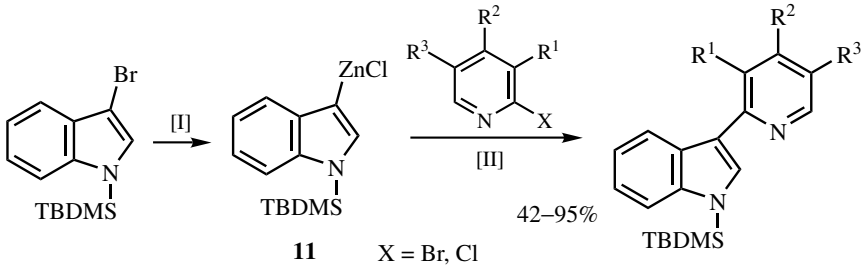


Ar = Ph; 4-NO_2-, 4-COOEt, 4-MeO-, 3-COOEt, and 3-Me_2NCO-C_6H_4; 2-thienyl 2-pyridinyl, 6-Me_2NCO-2-pyridinyl, 4-Me_2NCO-6-Me-2-pyrimidinyl

[I] (i) *t*-BuLi, THF, −70 °C, (ii) $ZnCl_2$, THF, −70 °C to r.t.; [II] 5 mol % $Pd(PPh_3)_4$, THF, rfx, 11–18 h.

Scheme 6

(1-TBDMS-3-indolyl)zinc chloride **11** has been coupled with 2-halogenopyridines carrying alkyl, methoxy, methoxycarbonyl, nitro, and hydroxy groups to yield the corresponding 3-(2-pyridinyl)indoles (**Scheme 7**). Another series of 3-(heteroaryl)indoles (pyrazinyl, furyl, thienyl, indolyl) has similarly been prepared from the indolylzinc substrate **11**. When the indole is *N*-protected as a sulfonyl derivative, the intermediate 1-(benzenesulfonyl)-3-lithioindole easily suffers rearrangement to the 2-lithio isomer. The 1-TBDMS-3-lithioindole is stable toward this rearrangement. The TBDMS-protecting group has therefore been recommended for use in cross-coupling reactions with metaloindoles. The silyl group is removed after the reaction by fluoride salts in the usual manner or under acidic conditions.[9]



X = Br, Cl

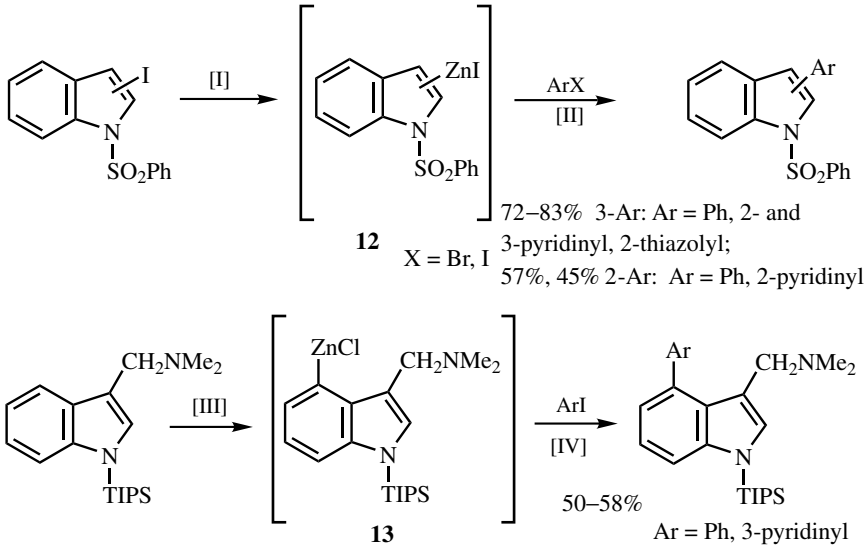
R^1, R^2, R^3 = H, Me, Et, OMe, OH, COOMe, NO_2

[I] (i) *t*-BuLi, THF, −78 °C, (ii) $ZnCl_2$, THF, 25 °C; [II] 2 mol % $Cl_2Pd(PPh_3)_2$, DIBAH, THF, rfx, 4 h.

Scheme 7

Basic lithium species as intermediates are avoided by direct zincation of an organo halide. It has been claimed that metallation in the 3-position in indoles is best effected by oxidative addition of zinc to a 3-iodide (**Scheme 8**). In the formation of the metallated species **12** from 3-iodo-*N*-benzenesulfonylindole, no rearrangement to the 2-isomer was

observed. The 2-iodo isomer reacts similarly, but the yield of coupled product was slightly lower. With a strongly directing metallation group in the 3-position, initial metallation is in the *peri*-vicinal position in the phenyl ring, that is, in the 4-position. The zincated intermediate **13** is subsequently coupled with aryl halides.[10]



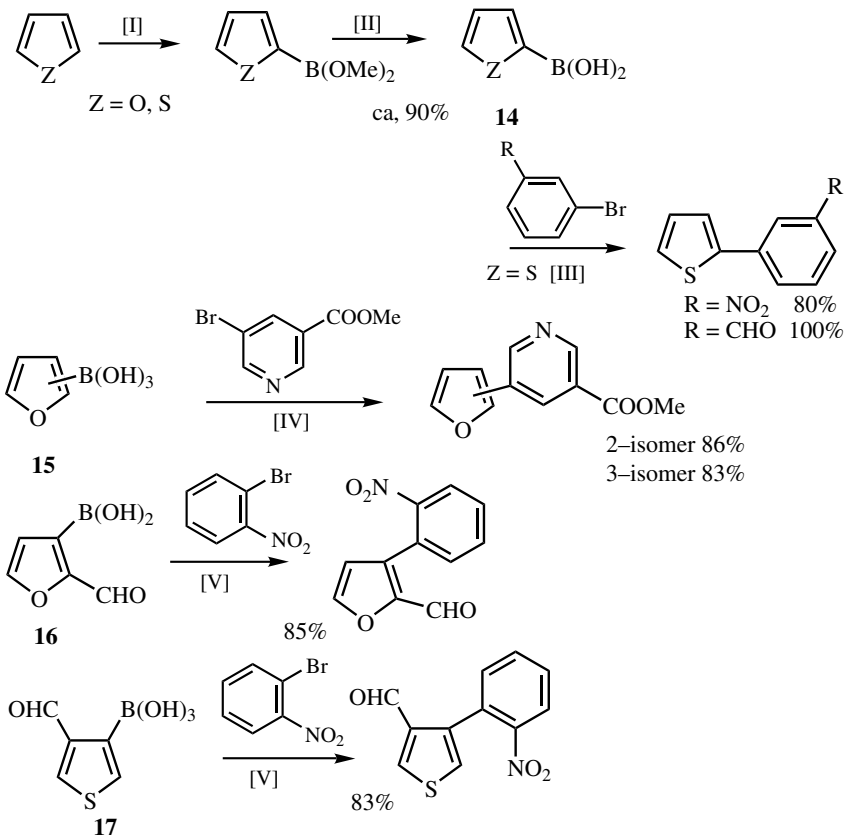
[I] Zn*, THF, r.t., 1–2 h; [II] 5 mol % $Pd(PPh_3)_4$, THF, r.t., 18 h; [III] (i) *t*-BuLi, –70 °C, (ii) $ZnCl_2$, –70 °C; [IV] 5 mol % $Pd(PPh_3)_4$, THF, rfx, 24 h.

Scheme 8

Boron Derivatives. Lithiation and metal–metal exchange in thiophene or furan give 2-boronic acids **14** for coupling with bromobenzenes (**Scheme 9**).[7] 2- or 3-Furanboronic acids **15** can be coupled with 5-bromonicotinic acid methyl ester.[11] 2- or 3-Thiopheneboronic acids have been coupled to 5-bromothiophene to yield the corresponding bithienyls in good yields.[12] 2-Formyl-3-furanboronic acid **16** under Suzuki conditions was coupled to bromobenzenes carrying an *o*-nitro or *o*-acetamido substituent.[13] The reaction proceeds equally well for the regioisomeric 3-formylthiophene **17**.[14]

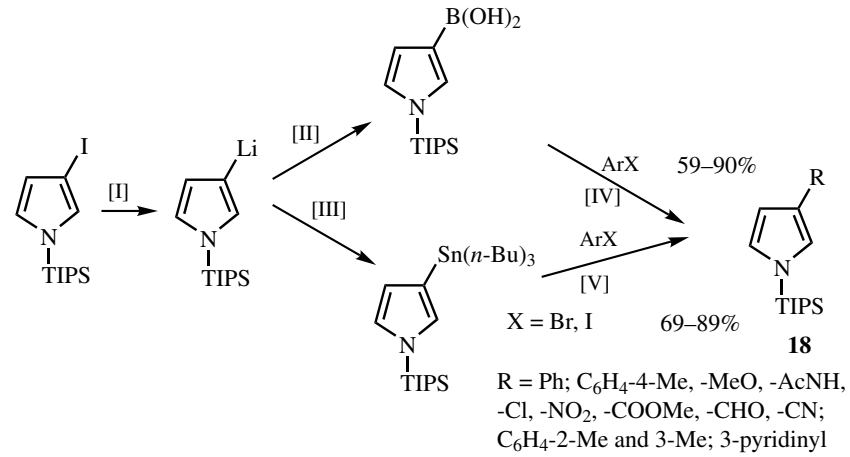
3-Arylpyrroles are available from 3-iodopyrroles (**Scheme 10**). Lithiation in the 3-position in 1-(triisopropylsilyl)-3-iodopyrrole followed by reaction of the lithio species with trimethyl borate and hydrolysis of the product gives the boronic acid. Coupling of the crude boronic acid with aryl halides under Suzuki conditions leads to the formation of 3-arylpyrroles **18**. Stannyl derivatives of pyrrole, prepared in a similar manner, gave comparable yields. The silyl deprotection was by tetrabutylammonium fluoride in THF.[15] *N*-Protection of 3-bromoindole, lithiation, and subsequent boronation gave boronic acid substrates **19** for cross-coupling with substituted 5-bromo- or 5-iodoimidazole.[16]

In the 2-position, the Suzuki coupling of *N*-Boc-pyrrole-2-boronic acid with phenyl iodide gave a moderate yield of the 2-phenyl product **20** (**Scheme 11**). With bromobenzene the yield was low. The best results were obtained with π-deficient arenes. The same coupling with indole derivatives gave even lower yields of arylated products. Homocoupling of the heterocycle is responsible for the major by-product. The boronic acid group

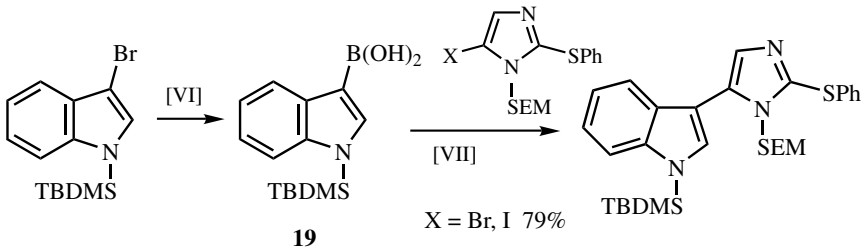


[I] (i) *n*-BuLi, THF, −10 °C to r.t., (ii) $B(OMe)_3$, −90 to −10 °C; [II] 30% HCl, THF, H_2O, −30 °C, 30 min; [III] 3 mol % $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, rfx, 30–45 min; [IV] 3 mol % $Pd(OAc)_2$ P(*o*-tol)$_3$, NEt_3, DMF, 100 °C, 2-3h; [V] 3 mol % $Pd(PPh_3)_4$, DME, H_2O, $NaHCO_3$, rfx, 1 h.

Scheme 9



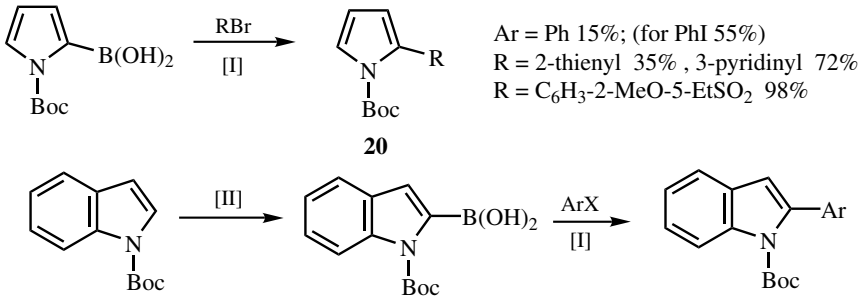
Scheme 10



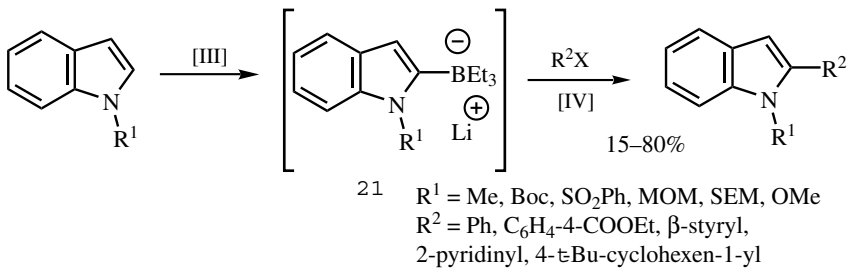
19

[I] *t*-BuLi, THF, −78 °C; [II] (i) $B(OMe)_3$, THF, −78 °C, (ii) MeOH, H_2O, −78 °C to r.t.; [III] $(n\text{-Bu})_3SnCl$, THF, −78 °C to r.t.; [IV] 5–10 mol % $Pd(PPh_3)_4$, benzene, MeOH, 2 M aq. Na_2CO_3, rfx, 10–48 h; [V] 10–17 mol % $Pd(PPh_3)_4$, dioxane, rfx, 24–40 h; [VI] (i) *n*-BuLi, THF, −78 °C, (ii) $B(OMe)_3$, (iii) MeOH-H_2O; [VII] 10 mol % $Pd(PPh_3)_4$, Na_2CO_3, MeOH, benzene, rfx, 15 h.

Scheme 10 (*Continued*)



20



21 R^1 = Me, Boc, SO_2Ph, MOM, SEM, OMe
R^2 = Ph, C_6H_4-4-COOEt, β-styryl, 2-pyridinyl, 4-tBu-cyclohexen-1-yl

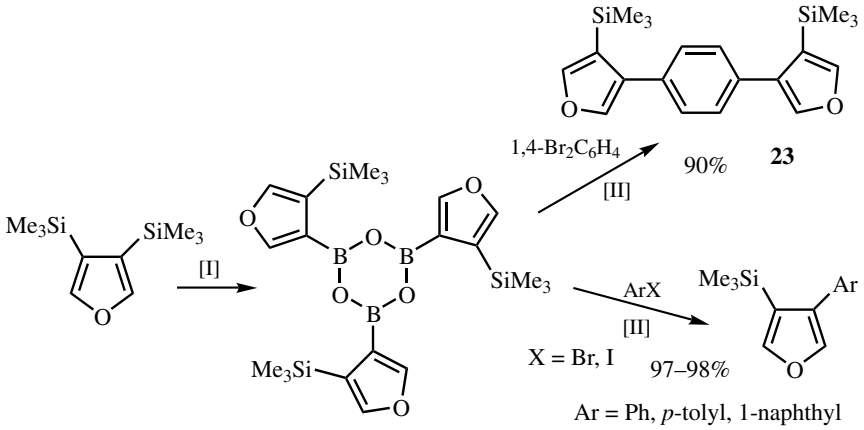
[I] 5 mol % $Pd(PPh_3)_4$, Na_2CO_3, H_2O, DME, rfx, 0.5–18 h; [II] (i) LiTMP, THF, −78 °C, (ii) $B[O(i\text{Pr})]_3$, (iii) H^+, H_2O; [III] (i) n or tBuLi, THF, −78 °C, (ii) BEt_3; [IV] 5 mol % $Cl_2Pd(PPh_3)_2$, THF, 60 °C, 0.5–2 h.

Scheme 11

is introduced by lithiation of *N*-protected indole, which is subsequently reacted with triisopropyl borate.[17] Lithiation and treatment of *N*-protected indoles with triethylboron gave *N*-substituted triethyl(2-indolyl)borates **21** for Suzuki coupling with aryl halides. Methoxymethyl (MOM) as *N*-protecting group suffered reduction. The benzenesulfonyl group was inferior for *N*-protection.[18]

The Diels–Alder reaction of equimolar quantities of bis(trimethylsilyl)acetylene and 4-phenyloxazole gives ready access to 3,4-bis(trimethylsilyl)furan, which undergoes *ipso* monosubstitution when treated with boron trichloride (**Scheme 12**). Hydrolysis of the

product gives the trimeric anhydride of the boronic acid, a boroxine **22**. The boroxine smoothly undergoes coupling reactions under Suzuki conditions to furnish the arylated product. A phenyl bridged dimeric product **23** is formed with 1,4-dibromobenzene.[19]



[I] (i) BCl_3, CH_2Cl_2, −78 to 0 °C, (ii) 1 M aq. Na_2CO_3; [II] 10 mol % $Pd(PPh_3)_4$, Na_2CO_3, MeOH/toluene, rfx, 3–6 h.

Scheme 12

Magnesium Derivatives. Lithiation and metal–metal exchange with a magnesium halide in either *N*-methylpyrrole, furan, or thiophene give the organomagnesium substrates **24** and **25** for Pd-catalyzed cross-coupling (**Scheme 13**).[7] The method has been adapted for the preparation of the alternating thiophene–pyridine chain **26**.[20]

B.i.b. *Alkenylation*

Tin Derivatives. Indole, *N*-protected by the (trimethylsilyl)ethoxymethyl group, is alkenylated as a 2-stannane **27** with vinyl bromides (**Scheme 14**). The coupling also proceeds readily with complex heterocycles as exemplified with the structures **28** and **29**.[5]

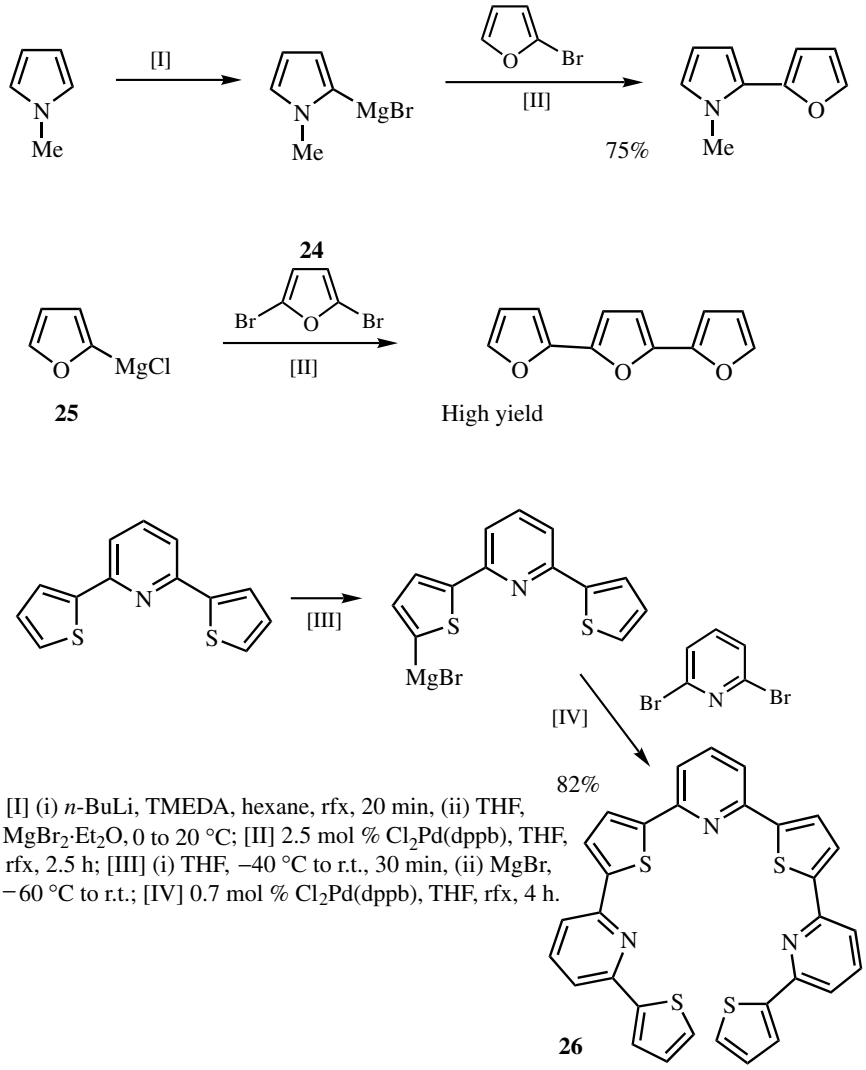
3,4-Bis(tri-*n*-butyl)stannylfuran or the 3-monostannyl derivative is available by a Diels–Alder reaction between bis(tri-*n*-butylstannyl)acetylene and 4-phenyloxazole. Either substrate, **30** or **31**, undergoes alkenylation when reacted with *trans*-β-bromostyrene (**Scheme 15**).[21]

B.i.c. *Alkynylation: Allenes*

Boron Derivatives. Alkynylation is commonly effected between a metallated terminal alkyne and a halogeno- or triflyloxyheterocycle. In the present case it is the heterocycle that is metallated. The coupling leads to allene derivatives **32** (**Scheme 16**).[22]

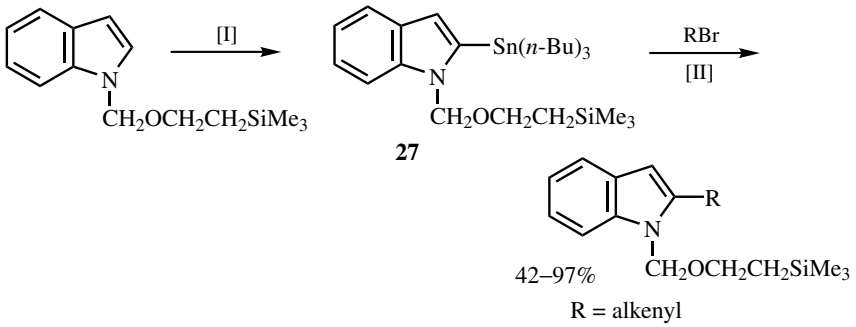
B.i.d. *Alkylation*

Tin Derivatives. A regiocontrolled method for construction of substituted benzofurans, dibenzofurans, benzothiophenes, and dibenzothiophenes uses 4-chloro-2,3-disubstituted-2-cyclobutenones as reactants together with a heterocycle (**Scheme 17**). In the construction

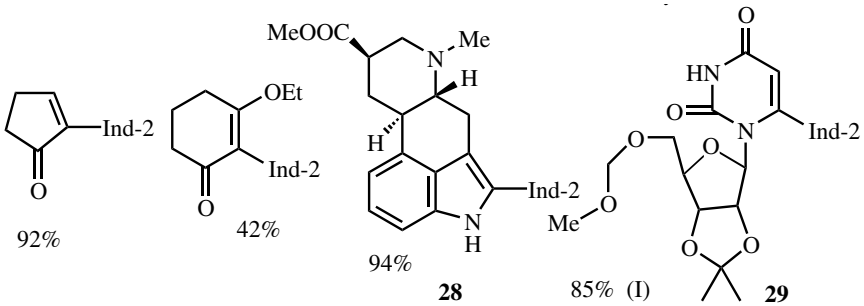


[I] (i) *n*-BuLi, TMEDA, hexane, rfx, 20 min, (ii) THF, $MgBr_2{\cdot}Et_2O$, 0 to 20 °C; [II] 2.5 mol % $Cl_2Pd(dppb)$, THF, rfx, 2.5 h; [III] (i) THF, −40 °C to r.t., 30 min, (ii) MgBr, −60 °C to r.t.; [IV] 0.7 mol % $Cl_2Pd(dppb)$, THF, rfx, 4 h.

Scheme 13

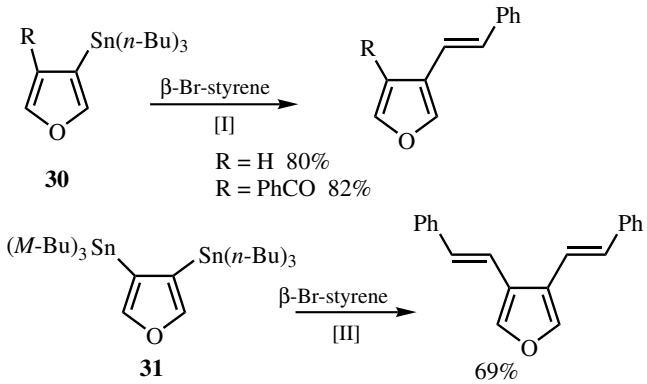


Scheme 14 (*Continued*)



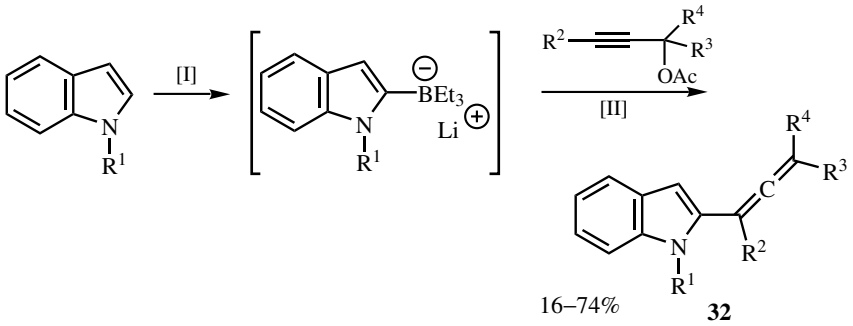
[I] (i) *n*-BuLi, THF, −10 °C, (ii) $(n\text{-Bu})_3$SnCl, THF, −20 °C; [II] 10 mol % $Pd(PPh_3)_4$ DMF, 110 °C, 1–72 h.

Scheme 14 (*Continued*)



[I] 5 mol % $[(C_3H_5)PdCl]_2$, HMPA, 60 °C, 23 h (R = PhCO, 2 h); [II] 4 mol % $[(C_3H_5)PdCl]_2$, HMPA, r.t., 1 h.

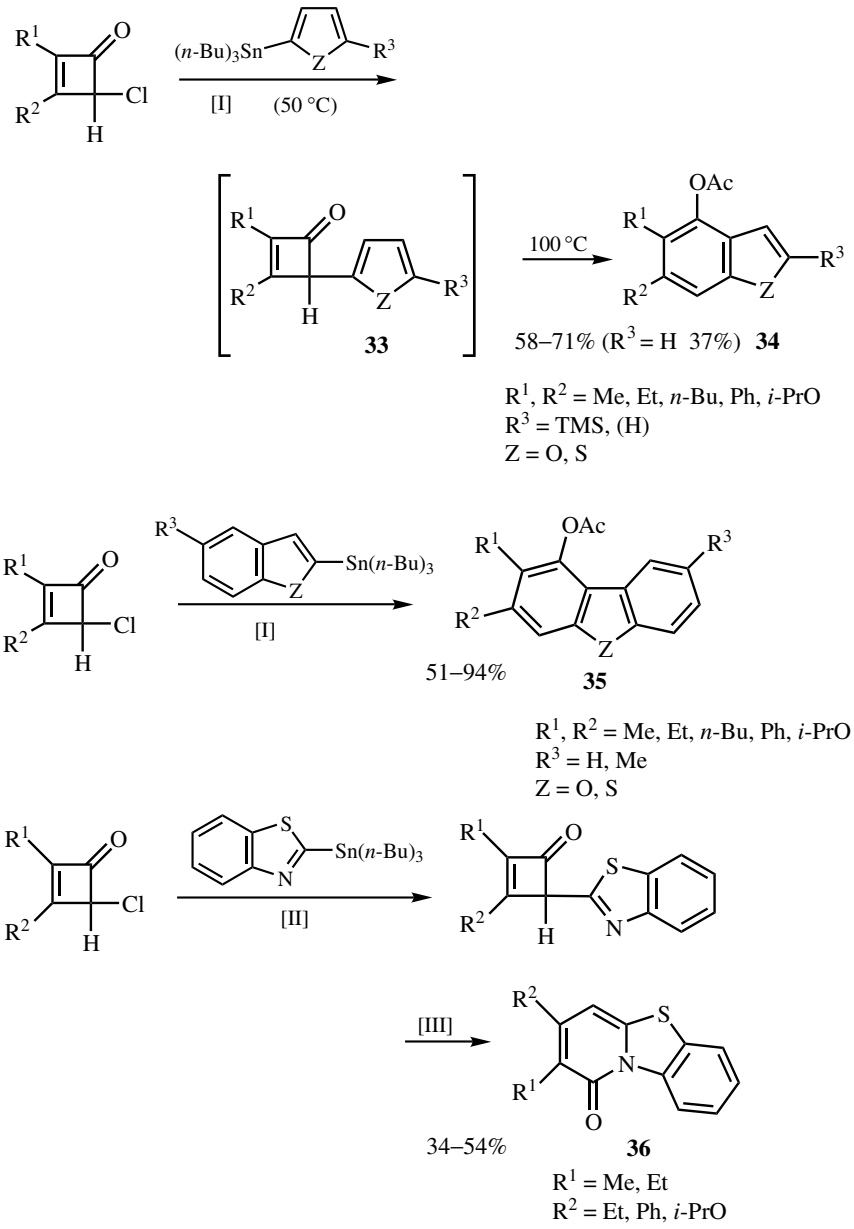
Scheme 15



R^1 = Me, Boc, OMe; R^2 = H, Me, Ph, COOMe, TMS, CH_2OTHP;
R^3–R^4 = $(CH_2)_5$, $(CH_2)_2N(Boc)(CH_2)_2$; R^3, R^4 = Me, $(CH_2)_2CH{=}CH_2$, $(CH_2)_3Cl$

[I] (i) *n*- or *t*-BuLi, −78 °C to 0 °C, (ii) BEt_3, −78 °C to 0 °C; [II] 10 mol % $Pd(PPh_3)_4$, $Cl_2Pd(PPh_3)_2$, $Pd_2(dba)_3{\cdot}CHCl_3/PPh_3$, $Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(OAc)_2$, $Cl_2Pd(MeCN)_2$, THF, 60 °C, 30 min.

Scheme 16



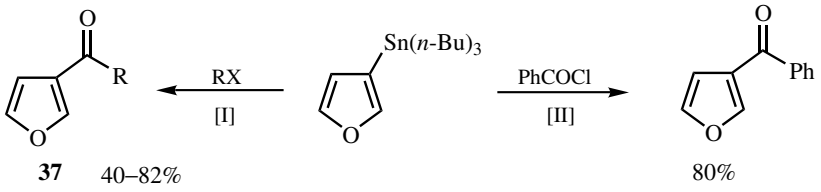
[I] (i) 5 mol % $Cl_2Pd(PhCN)_2$, 10 mol % TFP, dioxane, 50 °C (4–12 h), 100 °C (4 h), (ii) Ac_2O, pyridine; [II] 2.5 mol % $Pd_2(dba)_3$, 10 mol % TFP, toluene, 60 °C, 3–8 h; [III] **r**fx, 5–14 h.

Scheme 17

of substituted benzothiophenes or benzofurans, the initial reaction is a Pd-catalyzed coupling between 4-chloro-2,3-disubstituted-2-cyclobutenones and a 2-stannylthiophene or -furan. The product from the Stille cross-coupling with 4-chlorocyclobutenones is an alkylated heterocycle **33**, which is not isolated, but the reaction mixture is heated to 100 °C when a rearrangement takes place with formation of the benzannulated heterocycle **34**, presumably via a ketene-like intermediate. Relying on the control inherent in the construction of 4-chloro-2,3-disubstituted-2-cyclobutenones, regioisomeric substituted heteroarenes can be prepared. Several annulated heterocyclic systems including **35** and **36** have been prepared by this methodology.[23],[24]

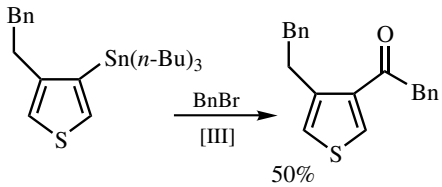
B.i.e. *Carbonylation and Acylations*

Tin Derivatives. 3-(Tri-*n*-butylstannyl)furan can be converted into a 3-furyl ketone **37** either by a Stille-type coupling under CO pressure or by acylation with an acid chloride (**Scheme 18**).[25] When 3-(phenylethyl)-4-(tri-*n*-butylstannyl)thiophene was allowed to react with benzyl bromide under an atmosphere of CO, formation of the carbonylated product **38** was accompanied by 13% yield of the symmetrical ketone, bis[4-(phenylethyl)thiophen-3-yl] ketone.[26] In 3,4-bis(tri-*n*-butylstannyl)furan **39** selective monoacylation can be achieved with acid chlorides. The ketones can subsequently be further carbonylated.[25]



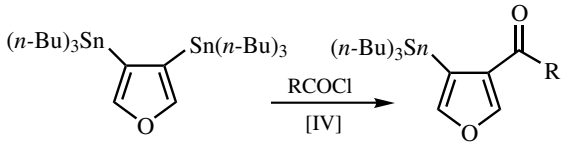
37 40–82% 80%

R = Ph, *n*-Bu, PhCH=CH, *n*-hexCH=CH



50%

38

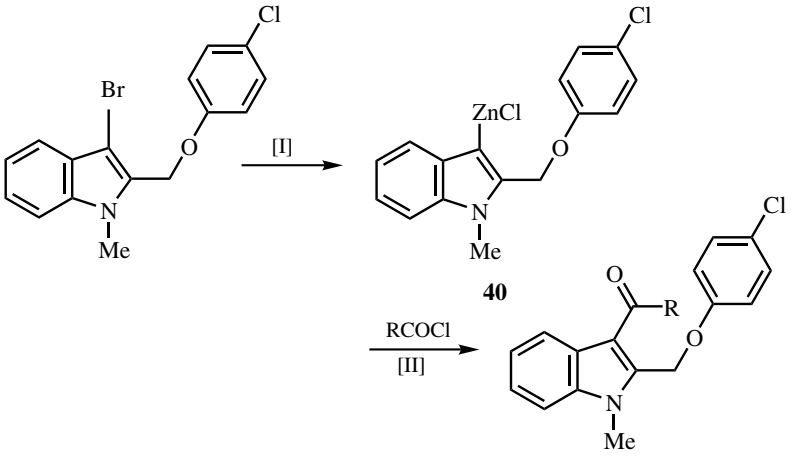


39

[I] 4 mol % $Cl_2Pd(PPh_3)_2$ or 7 mol % $Pd(PPh_3)_4$, THF, CO (30 psi), 50 °C, 2 d; [II] 4 mol % $Pd(PPh_3)$ THF, 60 °C, 2 h; [III] 10 mol % $Pd(PPh_3)_4$, CO (25–30 psi), THF, 50–60 °C, 2 d; [IV] 4 mol % $Cl_2Pd(PPh_3)_2$, THF, 65–80 °C, 8–24 h.

Scheme 18

Zinc Derivatives. 3-Acylindoles are formed by Pd-catalyzed coupling of a 1,2-disubstituted 3-indolylzinc chloride **40** with a number of acid chlorides to give the corresponding ketones (**Scheme 19**). The method is recommended for the preparation of acid-sensitive 3-acylindoles. The 3-lithio compound was prepared from the 3-bromide and zincated by means of zinc chloride. The palladium catalyst was prepared *in situ* by treating a suspension of palladium dichloride with *n*-BuLi.[27]



61–74% R = Me, Bn, *n*-Pr, Ph
33% for R = CH_2Cl

[I] (i) *t*-BuLi, THF, −78 °C, (ii) $ZnCl_2$, THF, −78 °C to r.t.; [II] (i) 10 mol % $Cl_2Pd(PPh_3)_2$, *n*-BuLi, r.t.,10 min, (ii) add RCOCl, −35 °C to 0 °C, 2 h.

Scheme 19

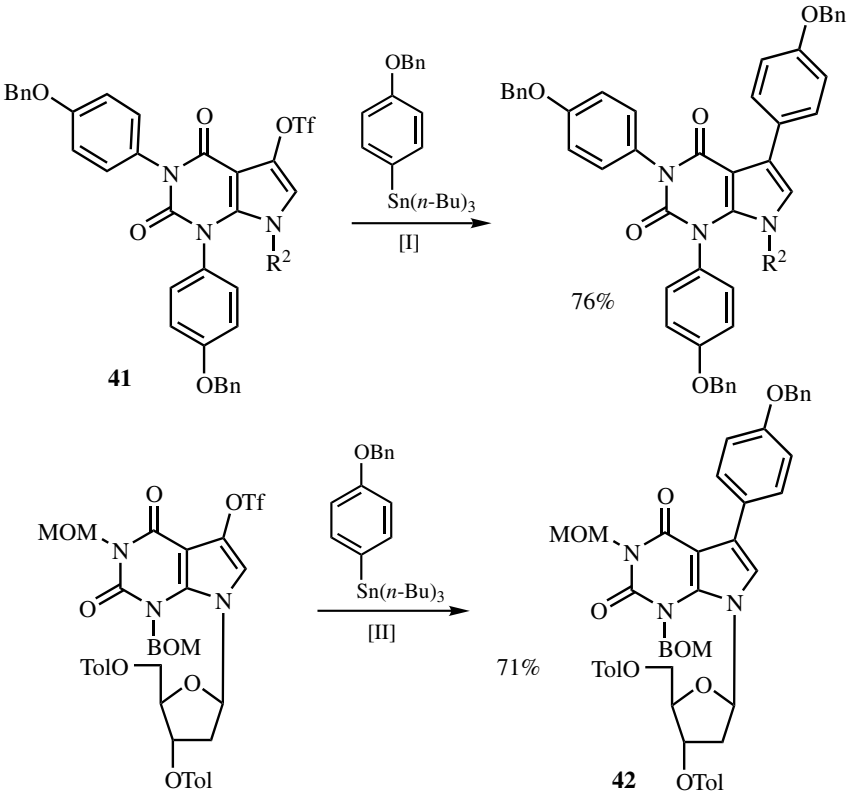
B.ii. Halogeno- or Triflyloxy-Substituted Five-Membered Ring Systems

B.ii.a. *Arylation*

Tin Reagents. The *N*-protected triflyloxy derivative **41** of pyrrolo[2,3-*d*]pyrimidine when reacted with an arylstannane affords 5-aryl derivatives (**Scheme 20**).[28] A closely related reaction has been used in the preparation of the 5-substituted β-2′-deoxyribosylpyrrolo[2,3-*d*]pyrimidines **42** from the corresponding C-5 triflate.[29]

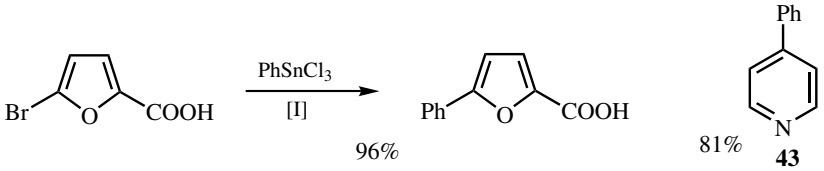
Stille couplings involving heterocycles have been effected in aqueous solution using a water-soluble catalyst, which was generated *in situ* from $PdCl_2$ and KOH (**Scheme 21**). Whereas halogen substituents on tin strongly retard the Stille reaction in organic media, the opposite effect was seen in aqueous media. It would appear that hydrolysis of the $RSnCl_3$ reagent facilitates both solubilization and C—Sn bond activation. Coupling was reported into the 5-position in furan-2-carboxylic acid as well as into the 4-position in pyridine **43**.[30]

Zinc Reagents. Negishi coupling between 2-iodofuran and phenylzinc chloride is a good reaction but the same reaction appears to fail when 2-bromofuran is used as reagent (**Scheme 22**).[31] Coupling between 2,5-dibromothiophene and 2-furylzinc chloride provides the dicoupled product **44** in high yield.[7]



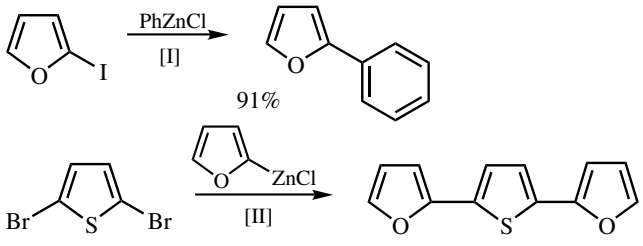
[I] 4.5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 9 mol % P(2-furyl)$_3$, $ZnCl_2$, NMP, 55 °C, 24 h;
[II] 10 mol % Pd_2dba_3, P(2-furyl)$_3$, NMP, 55 °C, 16 h.

Scheme 20



[I] 0.5–3 mol % $PdCl_2$, 2–12 mol % PhPdP(*m*-$C_6H_4SO_3Na)_2$, 10% KOH, 90 °C, 3 h.

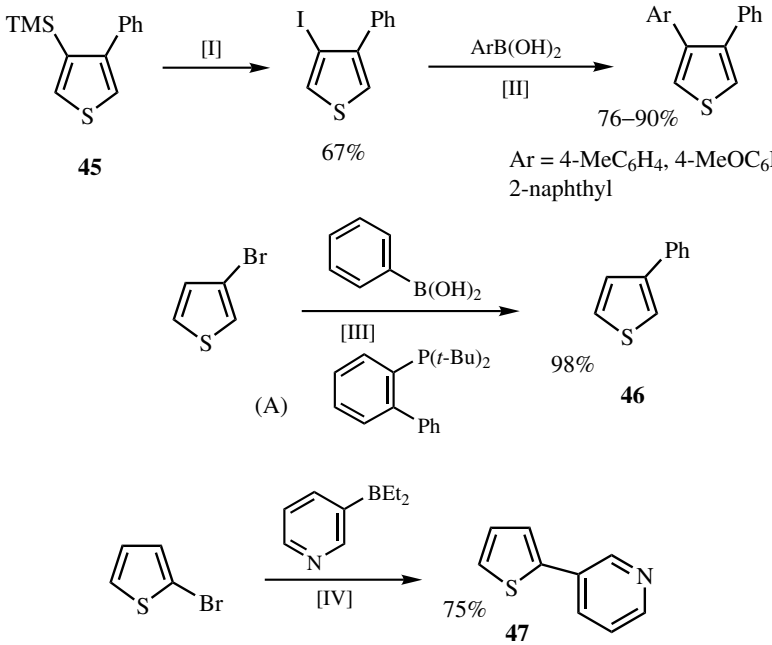
Scheme 21



[I] 5 mol % $Pd(PPh_3)_4$, THF, N.t.,5 h; [II] 3 mol % Cl_2Pd·dppb, THF, rfx, 2 h.

Scheme 22

Boron Reagents. Iodination of 3,4-bis(trimethylsilyl)thiophene followed by a Suzuki phenylation gives the monophenylated product 3-phenyl-4-trimethylsilylthiophene **45** (**Scheme 23**). After another *ipso*-iodination using iodine and silver trifluoroactetate and Suzuki coupling at the iodo carbon, 3,4-diarylated thiophenes are produced.[26] The same reactions have been effected in furans.[32]



[I] I_2, CF_3COOAg, THF, −78 °C to r.t.; [II] 5 mol % $Pd(PPh_3)_4$, Na_2CO_3, MeOH-PhMe (1:1), rfx, 5 h; [III] 1 mol % $Pd(OAc)_2$, 1 mol % (A), KF, THF, r.t., 17 h; [IV] 5 mol % $Pd(PPh_3)_4$, KOH, $(n\text{-Bu})_4NBr$, THF, rfx, 8 h.

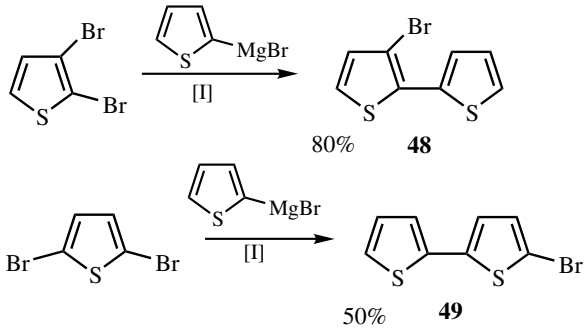
Scheme 23

A highly active palladium catalyst for Suzuki coupling reactions can be generated from palladium diacetate and 2-(di-*tert*-butylphosphino)biphenyl. Potassium fluoride is the preferred base for this system. The coupling of both bromides and chlorides proceeds at room temperature in excellent yields as exemplified by the preparation of 3-phenylthiophene **46**.[33] Cross-coupling between 2-bromothiophene and diethyl(3-pyridinyl)borane gives a pyridinyl 2-substituted thiopene **47**.[34]

Magnesium Reagents. Nickel catalysis is commonly used for cross-coupling reactions involving organomagnesium reagents. Palladium catalysis is often less efficient but more selective. In 2,3-dibromothiophene selective reaction in the 2-position gives the monocoupled product **48** (**Scheme 24**). Selectivity is rationalized by activation of the 2-position by the annular heteroatom. Monosubstitution can also be effected in 2,5-dibromothiophene to yield the bithienyl **49**.[7]

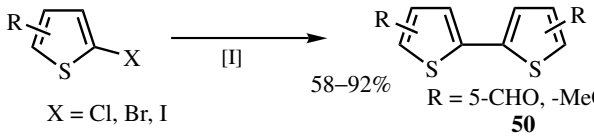
Homocoupling. Homocoupling corresponds to an arylation reaction with formation of symmetrical biheteroaryls from the same substrate. Homocoupling is frequently a side

reaction when heterocouplings are desired. Conditions can be chosen for exclusive homocoupling as for the preparation of bithienyls **50**.[35]



[I] 1.5 mol % $Cl_2Pd(dppf)$, Et_2O, 25 °C, 1.5 h.

Scheme 24



[I] 5 mol % $Pd(OAc)_2$, $NEt(i\text{-}Pr)_2$, $(n\text{-}Bu)_4NBr$, toluene, 105 °C, 4–24 h (2-Cl, 106 h).

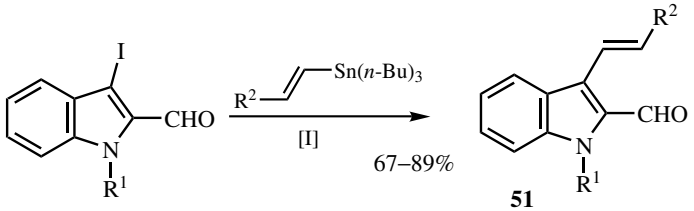
Scheme 25

B.ii.b. *Alkenylation*

Tin Reagents. In the π-excessive systems alkenylation has often been carried out with the metallated heterocycle (*vide supra*). Also widely used are Heck alkenylations (*vide infra*). Coupling of vinylstannanes with 3-iodoindoles was used in the preparation of 3-alkenylindoles **51** (**Scheme 26**).[36]

B.ii.c. *Alkynylation*

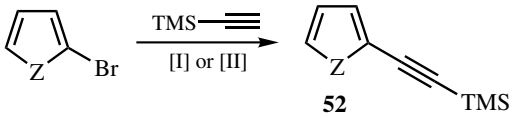
Copper Reactants. Application of the Pd/Cu-catalyzed cross-coupling, the Sonogashira reaction, with monosubstituted or protected acetylene gives rise to a variety of ethynyl-heteroarenes (**Scheme 27**). Reactions with trimethylsilylacetylene or phenylacetylene in



$R^1 = SO_2Ph$, MOM, R^2 = H, OEt

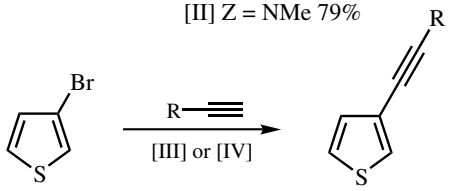
[I] 5 mol % $Cl_2Pd(PPh_3)_2$, Et_4NCl, DMF, 80 °C, 2 h.

Scheme 26



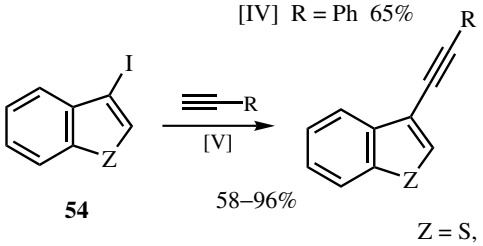
52

[I] Z = S 75%
[I] Z = O 74%
[II] Z = NMe 79%



53

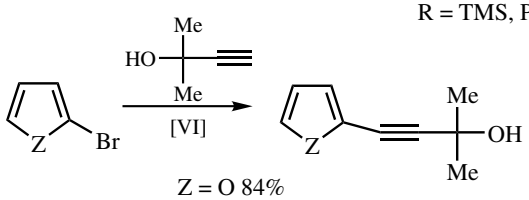
[III] R = TMS 88%
[IV] R = Ph 65%



54

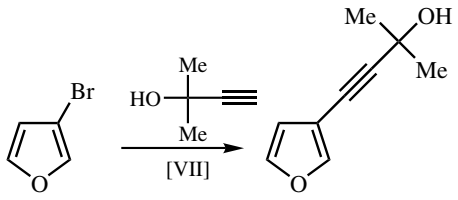
58–96%

Z = S, NMs
R = TMS, Ph, *n*-Bu, CH_2OH



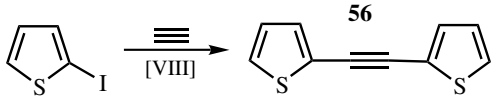
Z = O 84%
Z = S 95%

55



77%

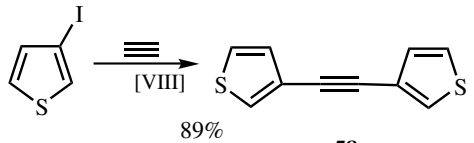
56



83%

57

Scheme 27 (*Continued*)



58

[I] 2.5 mol % $Cl_2Pd(PPh_3)_2$, PPh_3, CuBr, LiBr, NEt_3, rfx, 1–2 h; [II] 2.5 mol % $Cl_2Pd(PPh_3)_2$, CuBr, NEt_3, 75 °C, 3 h; [III] 2.5 mol % $Pd(PPh_3)_4$, PPh_3, CuBr, LiBr, piperidine, rfx, 20 min; [IV] 2.5 mol % $Pd(PPh_3)_4$, PPh_3, CuI, Et_2NH, EtOH, benzene, 45 °C, 30 min; [V] 4.5 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, DMF, 25 °C; [VI] 10 mol % $Pd(PPh_3)_4$, PPh_3, CuBr, NEt_3, 90 °C (rfx), 40–60 min; [VII] 10 mol % $Pd(PPh_3)_4$, PPh_3, CuBr, LiBr, $(i\text{-}Pr)_2NH$, piperidine, rfx, 5 h; [VIII] 3 mol % $Cl_2Pd(PPh_3)_2$, PPh_3, CuI, Et_2NH, rfx, 2–4 h.

Scheme 27 (*Continued*)

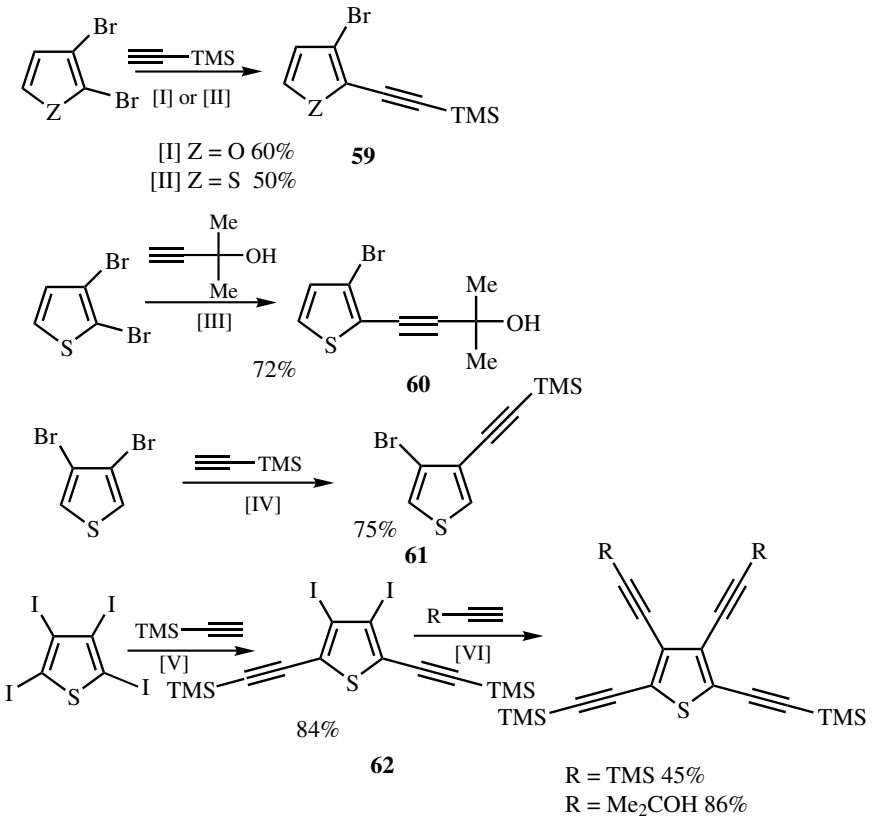
both the 2- and 3-positions of the π-excessive heterocycles furnish the ethynyl derivatives **52** and **53** in high yields.[37] 3-Iodobenzo[*b*]thiophene and *N*-protected indole **54** react similarly.[38] Acetylene is frequently protected as a monosilylated derivative. The monoadduct between acetylene and acetone can also be used for coupling of acetylene into π-excessive five-membered rings in either the 2- or the 3-position as in the preparation of the products **55** and **56**, respectively. Removal of the protecting group furnishes a monosubstituted acetylene. With free acetylene, dicoupling can be effected in excellent yields to give products with two thiophene units symmetrically bridged in the 2- or the 3-position, structures **57** and **58**, respectively.[37] Unsymmetrically bridged structures are best obtained in a two-step process starting from monoprotected acetylene.

Regioselectivity can be achieved in coupling reactions with 2,3-dibromothiophene or 2,3-dibromofuran (**Scheme 28**). The halogen next to the heteroatom is the more reactive. With silyl-protected acetylene, selective reaction in the 2-position in either heterocyclic system gives the coupling products **59**. The acetone-protected acetylene gave 72% of the 2-ethynylthiophene **60**. The reactivity is lowered after introduction of the first acetylene substituent. Therefore, the monocoupled silyl-protected acetylenic product **61** is accessible from 3,4-dibromothiophene.[37] In tetraiodothiophene the halogens in the α-positions are the more reactive in Sonogashira coupling. Thus, TMS-protected acetylene gave the 2,5-diethynyl product **62** in high yield. The latter can be further ethynylated in a second reaction step under similar conditions. The reaction with acetone-protected acetylene, that is, with 2-methyl-3-butyl-2-ol, proceeds even better (84%) in the tetraethynylation than with the silyl-protected reagent. The silyl groups are removed under mild alkaline conditions to furnish tetraethynylthiophene. Acetonyl deprotection requires more vigorous conditions.[39]

The Sonogashira coupling procedure is a high yielding process also in structurally complicated molecules (**Scheme 29**). Reaction between fully protected 5-triflyloxy β-2′-deoxyribosylpyrrolo[2,3-*d*]pyrimidines and *N*-(propargyl)trifluoroacetamide was used to prepare the alkynylated product **63**.[29]

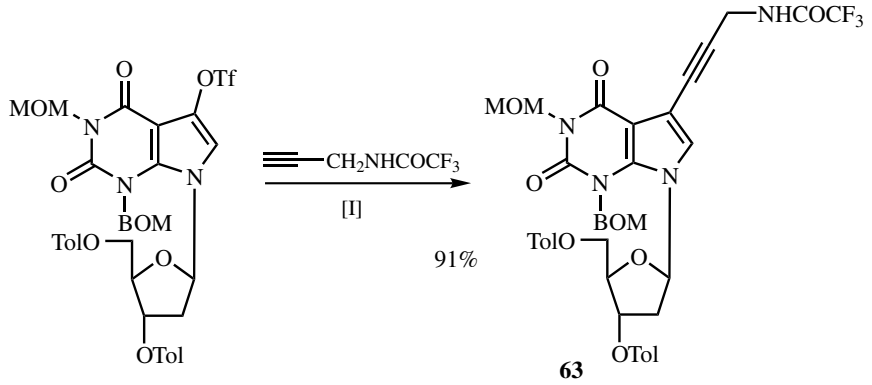
Tin Reagents. ipso-Monoiodination of 3,4-bis(trimethylsilyl)thiophene followed by Pd-catalyzed cross-coupling with stannylated acetylene gives the monalkyne **64**. Distannylated acetylene will give the alkyne substituted at both termini **65** (**Scheme 30**).[26]

Zinc Reagents. Coupling of heteroaryl iodides or bromides with ethynylzinc halides yields alkynylated heterocycles (**Scheme 31**). The ethynylzinc reagent can be prepared i*n situ* by addition of a zinc halide to the ethynylmagnesium halide, which is either



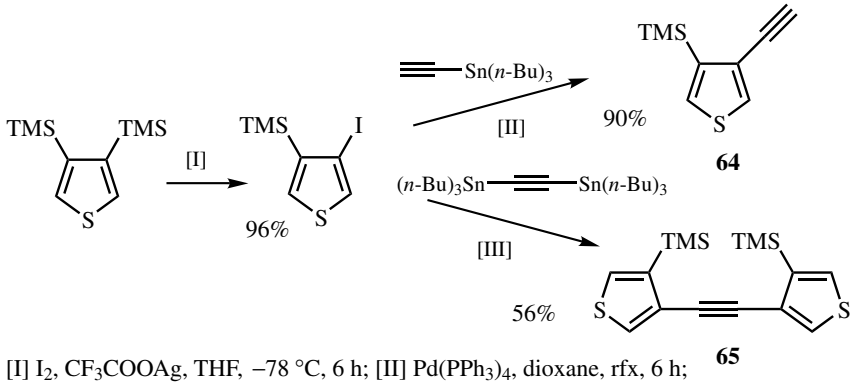
[I] 3 mol % $Pd(PPh_3)_4$, PPh_3, CuBr, LiBr, NEt_3, rfx, 1.5 h; [II] 3 mol % $Cl_2Pd(PPh_3)_2$, PPh_3,Cu $(i\text{-Pr})_2NH$, rfx, 2 h; [III] 3 mol % $Cl_2Pd(PPh_3)_2$, PPh_3, CuI, NEt_3, 50–80 °C, 3 h, [IV] 3 mol % $Cl_2Pd(PPh_3)_2$, PPh_3, CuI, Et_2NH, rfx, 3 h; [V] 5 mol % $Cl_2Pd(PhCN)_2$, PPh_3, CuI, $(i\text{-Pr})_2NH$, r.t. (12 h), rfx, 1 h; [VI] 10 mol % $Cl_2Pd(PhCN)_2$, PPh_3, CuI, $(i\text{-Pr})_2NH$, N.t. (4–12 h), rfx.

Scheme 28



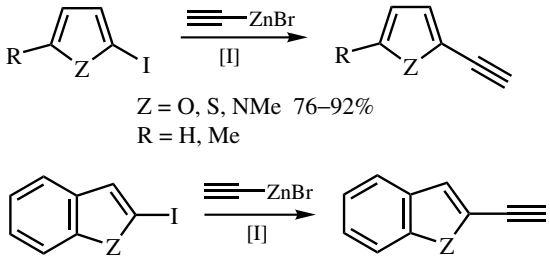
[I] 10 mol % $Pd(PPh_3)_4$, CuI, NEt_3, DMF, r.t., 4 h

Scheme 29



[I] I_2, CF_3COOAg, THF, −78 °C, 6 h; [II] $Pd(PPh_3)_4$, dioxane, rfx, 6 h; [III] $Pd(PPh_3)_4$, dioxane, Et_3N, 90 °C, 8 h.

Scheme 30



Z = O, S, NMe 76–92%
R = H, Me

Z = O, S 78%, 92% **66**

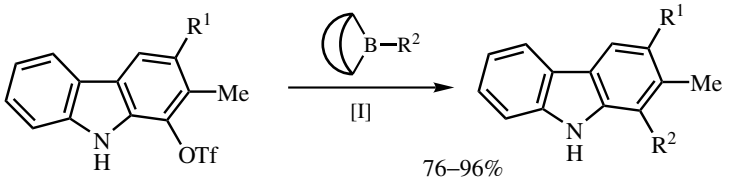
[I] 5 mol % $Pd(PPh_3)_4$, THF, 22 °C, 1–4 h.

Scheme 31

commercially available or readily prepared. Since Sonogashira coupling does not permit direct cross-coupling of acetylene itself in a selective manner, mainly due to competitive dicoupling, the Zn−Pd procedure offers a distinct advantage in the synthesis of terminal alkynes. Arenes containing an electron-rich aryl group are known to be less reactive in Pd-catalyzed coupling than those containing an electron-withdrawing group due to slower rates of oxidative addition. Using ethynylzinc halides, synthesis of arylethynes containing a π-excessive heteroaryl group proceeds exceptionally well. A variety of furan, thiophene, and benzannulated derivatives **66** have been prepared.[40]

B.ii.d. *Alkylation*

Boron Reagents. The transfer of an alkyl group from a stannane to a Pd(II) complex in the catalytic cycle normally requires vigorous conditions unless the alkyl group is specially activated. Alkyl groups are transferred more easily from an alkylzinc halide. Alkyl groups can also be transferred from boranes (**Scheme 32**). In carbazoles there is no heterocyclic ring position available for substitution. Carbosubstitutions are in a benzene ring and cross-coupling will therefore proceed in the same manner and under the same conditions as in other phenyl derivatives. When the triflate **67** was subjected to Suzuki coupling with 9-alkyl-9-BBN reagents, 1-alkylcarbazoles were formed.[36]



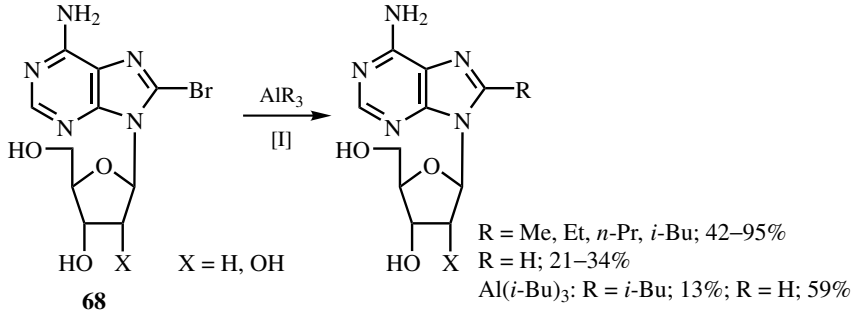
67

R^1 = H, OEt
R^2 = *n*-Hept, $(CH_2)_nCHMe_2$, *n* = 4–6

[I] 5–8 mol % $Cl_2Pd(dppf)$, NaOH, THF, 80 °C, 1.5–3 h; [II] 4 mol % $Pd(PPh_3)_4$ Na_2CO_3, DME, 100 °C, 1 h.

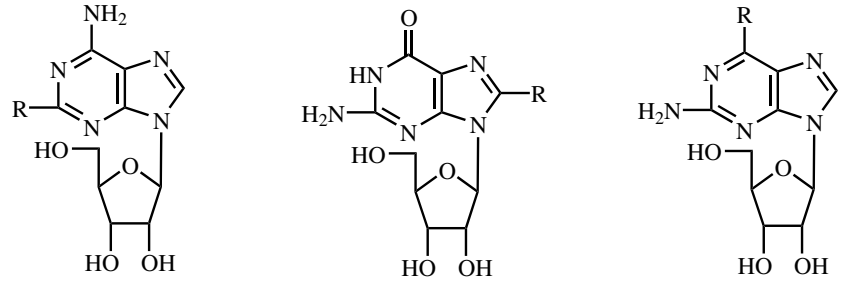
Scheme 32

Aluminum Reagents. Simple aluminum derivatives are good reagents for alkylations because the alkyl groups are readily transferable from alanes to the Pd(II) complexes in the catalytic cycle. This methodology has been used for the synthesis of *C*-alkylated purine nucleosides from halogenopurine nucleosides and trialkylalanes (**Scheme 33**). The coupling reaction for 8-bromoadenosine **68** itself failed. Reaction with TMS-protected



68

R = Me, Et, *n*-Pr, *i*-Bu; 42–95%
R = H; 21–34%
Al(*i*-Bu)$_3$: R = *i*-Bu; 13%; R = H; 59%



69 **70** **71**

R = Br
R = Me, Et, *n*-Pr
Al(*i*-Bu)$_3$: R = *i*-Bu; 34%; R = H; 43%

R = Br
R = Me 83% (24 h)

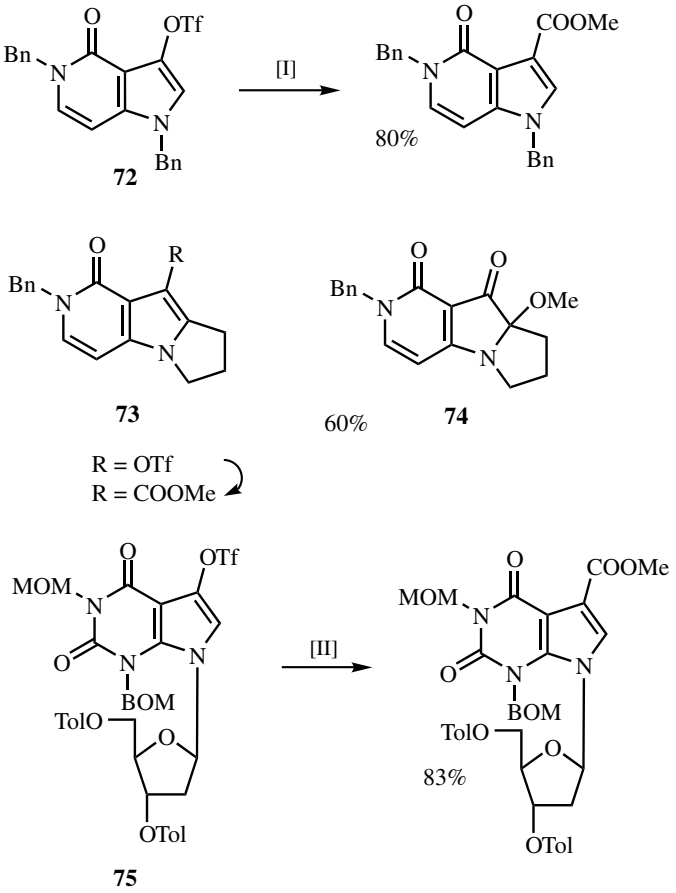
R = Cl
R = Me 70% (70 h)

[I] (i) HMDS, (ii) 5 mol % $PdCl_2$, PPh_3, THF, rfx, 2 h.

Scheme 33

8-bromoadenosine, however, led to the alkylated product when trimethylalane was the reagent. Excess of the alane was used. Other trialkylalanes reacted similarly to furnish the corrresponding 8-alkylpurine nucleosides. Debromination may lead to a side reaction. Debromination was especially pronounced in reactions with the bulky triisopropylalane. 2-Bromoadenosine and 8-bromoguanosine also gave the corresponding alkylated products, **69** and **70**. For alkylation in the electrophilic 6-position, the substrate was 2-amino-6-chloro-9-β-*D*-ribofuranosylpurine **71**.[41]

B.ii.e ***Carbonylation and Acylation.*** The keto function in pyrrolo[3,2-*c*]pyridin-4-ones and pyrido[3,4-*b*]pyrrolizidin-1-ones can be enolized and triflated to yield the substrates **72** and **73**, respectively (**Scheme 34**). Replacement of the triflyloxy group by carbonylation is effected with palladium catalysis. Reaction of the pyrido[3,4-*b*]-pyrrolizidin-1-ones **73** was complicated by formation of a by-product, namely, the 2-methoxy adduct **74**. In the latter case competitive palladium-assisted elimination of the triflyloxy group leads to an imminium intermediate, which adds a methoxy group as a

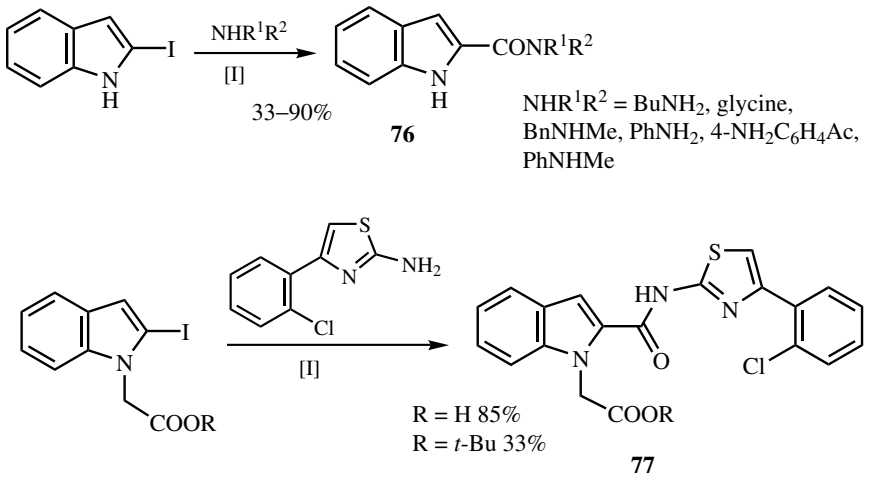


[I] 3 mol % $Pd(OAc)_2$, PPh_3 (2:9), NEt_3, CO (1 atm), DMF, MeOH, 65 °C;
[II] 10 mol % $Pd(OAc)_2$, PPh_3, NEt_3, CO (1 atm), DMF, MeOH, 68 °C, 2 h.

Scheme 34

nucleophile to form the by-product **74**.[42] Similarly, the triflated deazapurine nucleoside analog **75** can be carbonylated and esterified.[29]

Carbonylation of a 2-iodoindole in the presence of an amine provides a method for the preparation of indole-2-carboxamides **76** (**Scheme 35**). Unprotected indole was a better substrate than its Boc-protected derivative in this reaction. The methodology can also be used to construct more complex carbamates **77**.[43]



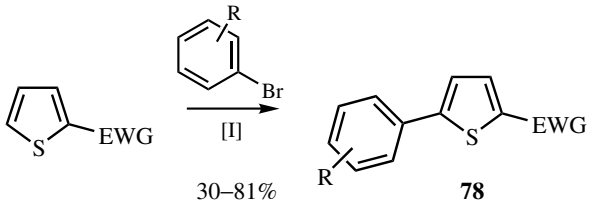
[I] 5 mol % $Cl_2Pd(PPh_3)_2$, N(*n*-Bu)$_3$, CO (1 atm), DMA, 115 °C, 10 min.

Scheme 35

B.ii.f. *Heck Reaction*

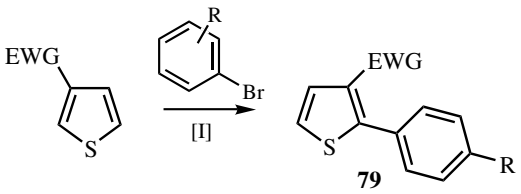
Addition into the Heterocycle. The regiochemistry in Heck-type arylation of 2- and 3-substituted thiophenes is affected by the nature of the thiophene substituent and its relative position (**Scheme 36**). Regiospecific substitution occurs in the 5-position when the heterocycle is α-substituted with an electron-withdrawing group **78**. An electron-withdrawing group in the thiophene 3-position largely directs the Heck substitution into the 2-position **79**. By-products result from substitution in the 4- and the 2,4-positions.[44] A number of Heck couplings into π-excessive heterocycles **80** have been effected using the π-deficient pyrazine ring substituted by a chlorine. Since all pyrazine positions are electrophilic, a chloro rather than a bromo or iodo derivative can be used for the coupling. Under the conditions of the reaction, some disubstitution into the furan, thiophene, or pyrrole may result **81**. Pyrrole and its *N*-methyl derivative behaved similarly, furnishing the monocoupled product in moderate yields; furan and thiophene reacted well. In all these cases the regiospecificity was such that the carbosubstitution was in the 2-position, next to the heteroatom as commonly seen in Heck reactions with a vinyl ether. Benzo[*b*]furan and benzo[*b*]thiophene behaved in the same manner with regioselective substitution into the 2-position **82**. With pyrrole *N*-acylated by the strongly electron-withdrawing benzenesulfonyl group **83**, however, the product was a mixture of the two regioisomers.[45] 5-Iodo- and 5-bromo-2,4-dimethoxypyrimidine also undergo the Heck substitution into thiophene. The reaction was effected under heterogeneous conditions in

aqueous media by heating the reactants in aqueous solution containing $(n\text{-Bu})_4NHSO_4$ and potassium carbonate. The yield of the Heck product **84** was 50% from the iodopyrimidine and 37% from the bromopyrimidine. When the iodopyrimidine and thiophene were heated at 150 °C in a pressure reactor (50 psi), the reaction took another course in that the thienylation was in the pyrimidine 6-position, the product being 6-(2-thienyl)-2,4-dimethoxypyrimidine **85**.[46]



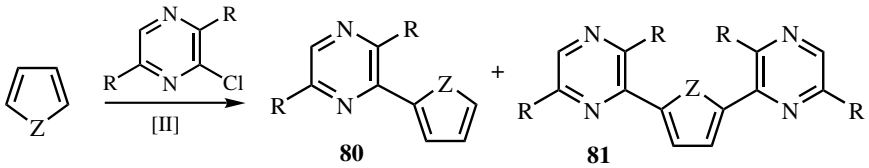
30–81% **78**

R = H, 4-MeO, 2- and 4-CF_3, and C_6H_4R = 1-naphthyl



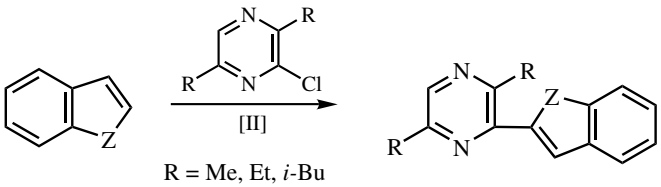
79

R = H, EWG = CHO 35%
R = OMe, EWG = CN 30%



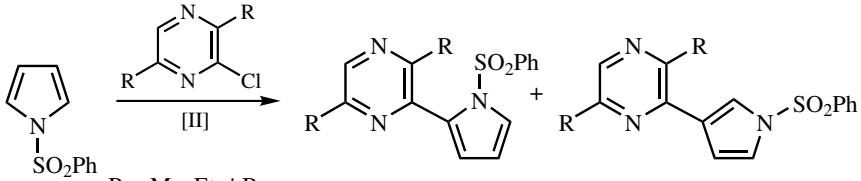
80 **81**

R = Me, Et, *i*-Bu Z = O, S 55–82% 0–22%
Z = NH, NMe 25–29% 14–27%



R = Me, Et, *i*-Bu

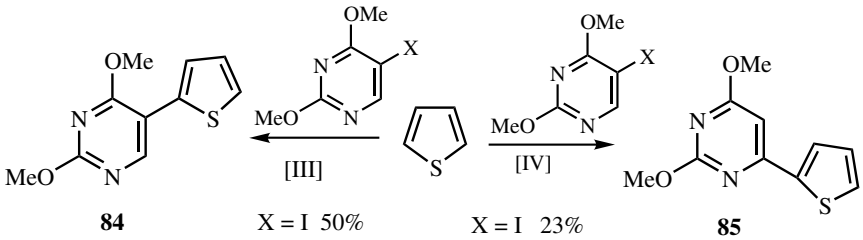
Z = O, S 45–72% **82**



83 R = Me, Et, *i*-Bu

R = Me, Et, *i*-Bu 40–44% (1:1–2:5)

Scheme 36



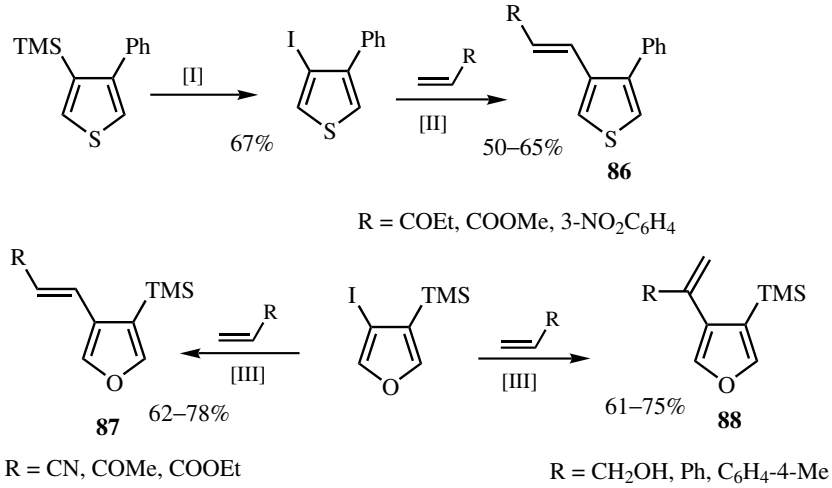
[I] 5 mol % $Pd(OAc)_2$, K_2CO_3, $(n\text{-}Bu)_4NBr$, MeCN, H_2O, 80 °C, 3–7 h (NO_2; 54 h); [II] 5 mol % $Pd(PPh_3)_4$, AcOK, DMA, rfx, 6 h; [III] 7 mol % $Pd(OAc)_2$, PPh_3, K_2CO_3, $(n\text{-}Bu)_4NHSO_4$, H_2O, 95 °C, 24 h; [IV] 7 mol % $Pd(OAc)_2$, PPh_3, K_2CO_3 $(n\text{-}Bu)_4NHSO_4, H_2O$, 150 °C, 50 psi, 24 h.

Scheme 36 (*Continued*)

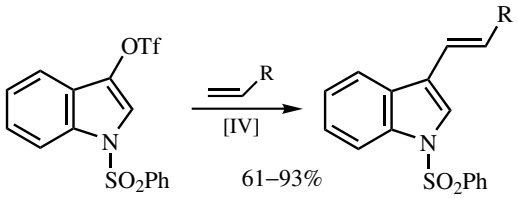
Addition by the Heterocycle. Under Heck conditions, 3-phenyl-4-vinylthiophenes **86** were formed from 3-iodo-4-phenylthiophene and ethyl vinyl ketone, methyl acrylate, and *m*-nitrostyrene (**Scheme 37**)[26] 4-Iodo-3-trimethylsilylfuran under similar Heck conditions with alkenes reacted in two regioselective manners. Alkenes with electron- withdrawing groups, such as methyl vinyl ketone and ethyl acrylate, gave exclusively *trans*-substituted alkenes **87**. Allyl alcohol, styrene, and 4-methylstyrene gave α,α-disubstituted products **88**.[47] 1-(Phenylsulfonyl)indol-3-yl trifluoromethanesulfonate under Heck conditions provides 3-vinylindoles **89**.[48] An excellent yield was reported for the reaction between the triflated deaza nucleoside **90** and ethyl acrylate.[29]

B.ii.g. *Annulation*

Heck Annulation. Intramolecular Heck reactions are useful for annulation in heterocyclic structures. *N*-(2-Iodobenzoyl)indoles or -pyrrole undergo Pd-catalyzed annulation to furnish

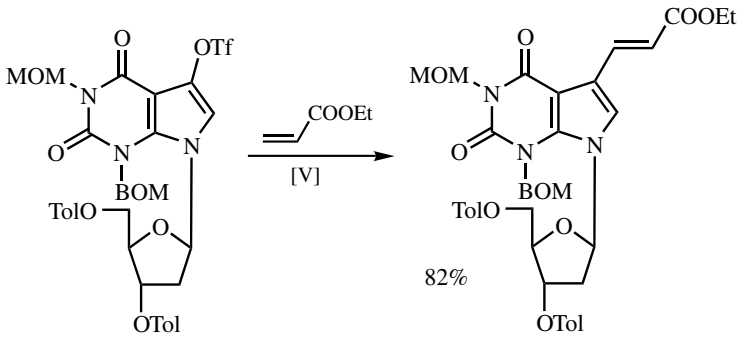


Scheme 37 (*Continued*)



89

R = COOMe, COOEt, COEt, CHO, Ph, H,



90

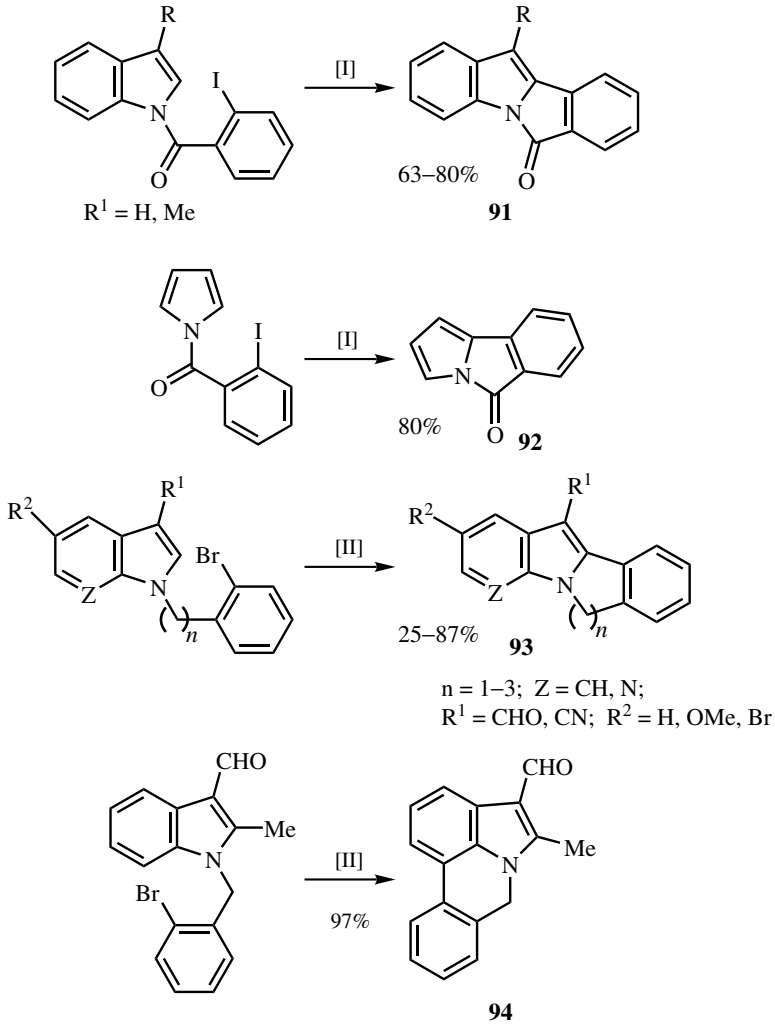
[I] I_2, CF_3COOAg, THF, −78 °C to r.t.; [II] $Pd(OAc)_2$, K_2CO_3, $(n\text{-}Bu)_4NI$, DMF, 90 °C, 8 h; [III] 5 mol % $Pd(OAc)_2$, NEt_3, rfx, 28 h; [IV] 3 mol % $Cl_2Pd(Ph_3)_2$ $(i\text{-}Pr)_2NEt$, DMF, 70–80 °C, 12–36 h; [V] 10 mol % $Cl_2Pd(PPh_3)_2$, PPh_3, NEt_3, DMF, MeOH, 90 °C, 17 h.

Scheme 37 (*Continued*)

the corresponding Heck products **91** and **92** (**Scheme 38**).[49] *N*-Alkarylindoles and 7-azaindole analogs furnish cyclic compounds under Heck conditions with the new carbon–carbon bond in the indole 2-position **93**. When the 2-position in the indole is blocked by methyl substitution, cyclization occurs into the 7-position in the benzene ring **94**.[50]

Indole-3-acetic acid derivatives can be prepared by the Heck cyclization of *N*-allyl substituted *o*-halogenoanilines.[51]–[53] The same concept has been used in the preparation of seleno- and thienopyrroles (**Scheme 39**). In this reaction *N*-Boc-protected *o*-iodoheteroarylamines were *N*-allylated with ethyl 4-bromocrotonate to form the substrate **95**. Pd-catalyzed ring closure in a one-pot reaction yielded *N*-Boc-protected thienopyrroles and selenopyrrole. The Boc group was readily removed thermally after adsorption on silica. Oxothienopyrroles were similarly prepared from appropriate carbamoyl derivatives **96**.[54]

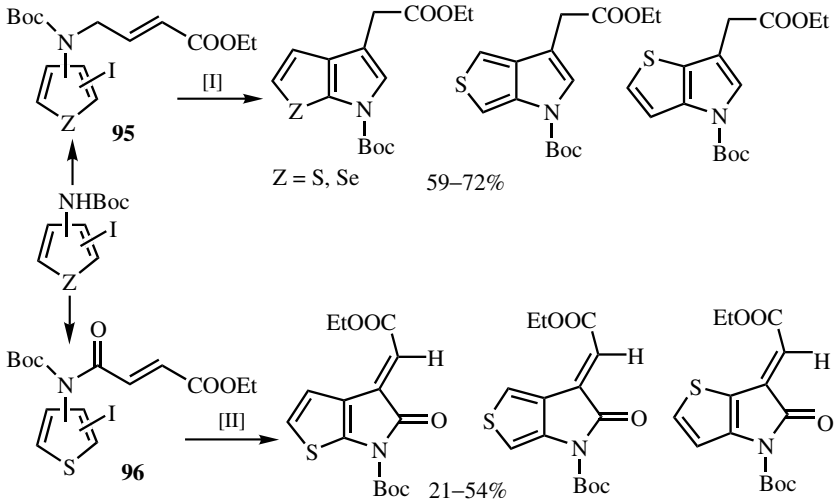
Alkylpalladium(II) species **97**, generated via initial palladium cyclization of an aryl iodide onto a proximate alkene, are highly reactive and will attack proximate aromatic or heteroaromatic rings, both electron rich and electron poor, leading to spirocycles **98** (**Scheme 40**). The second cyclization step onto the aromatic ring is expected to occur with *cis*-stereochemistry. The β-hydride elimination step normally occurs with *cis*-stereochemistry. This process is not possible in the present case. Similarly, formally forbidden eliminations are not uncommon especially when the Pd(II) species is located at a benzylic position and may involve prior stereomutation of the Pd(II) moiety or a slower *trans*-elimination.[55]



[I] 10 mol % $Pd(OAc)_2$, PPh_3, K_2CO_3, Et_4NCl, MeCN, rfx, 4–12 h;
[II] 6 mol % $Pd(PPh_3)_4$, KOAc, DMF, 110 °C, 1.5–10 h.

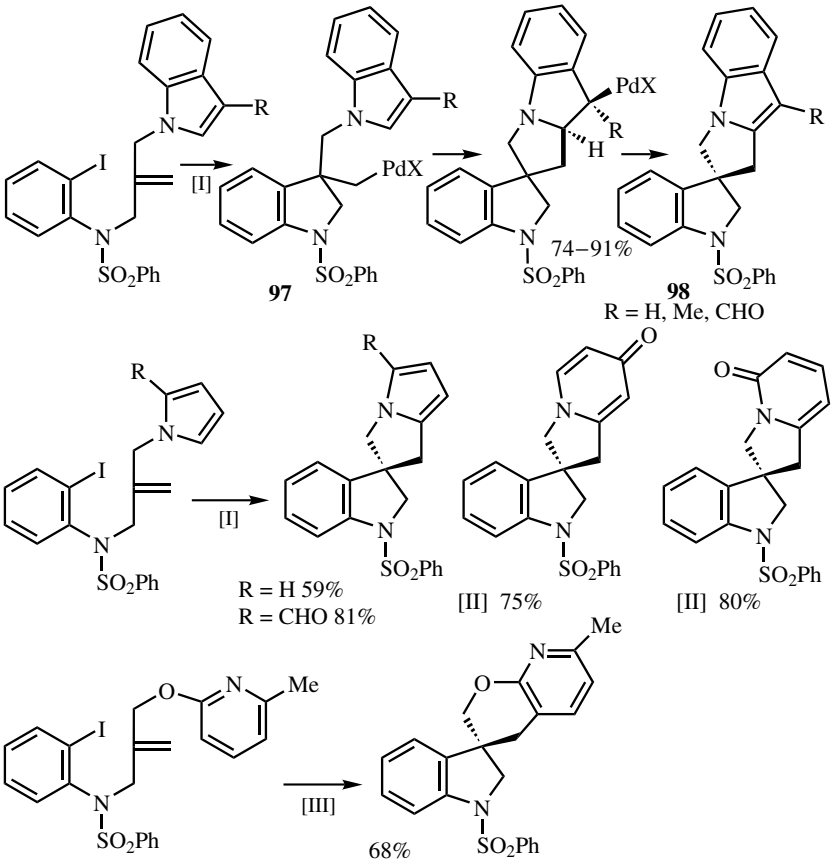
Scheme 38

Annulation Via Heterosubstituent. Several applications of the Larock synthesis of indoles have been published where heterocycles are used as substrate. In the Larock method for indol construction, Pd-catalyzed heteroannulation of internal alkynes using *ortho*-iodoaniline and its derivatives were used.[56] The methodology is well suited for adaption to heterocyclic systems (**Scheme 41**). Larock in his method for indole formation uses acetylenes with large protecting groups at the one terminus. A sterically demanding silyl group ends up adjacent to the nitrogen in the indole. The same methodology and findings were observed in the reaction between 3-amino-2-iodothiophenes and terminally silylated propargyl alcohol in the preparation of heteroannulated pyrroles **99**.[57]

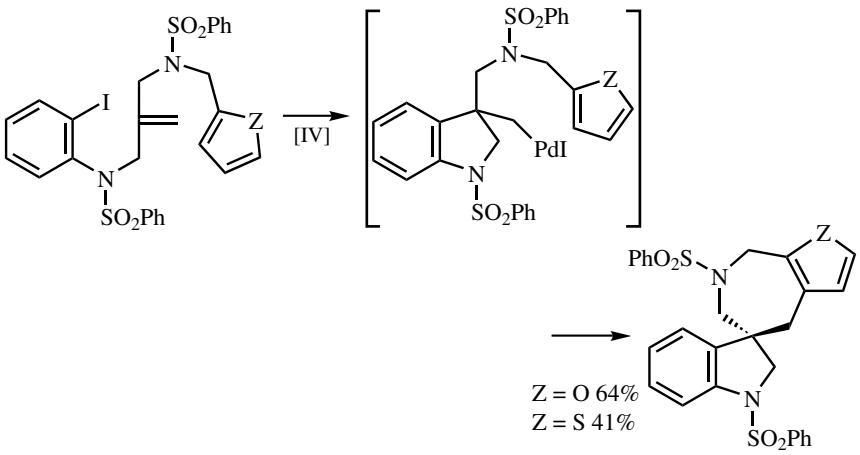


[I] 5 mol % $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, r.t. −65 °C; [II] 5 mol % $Pd(OAc)_2$, PPh_3, DMAP, TEA, THF, rfx, 5 h (40 °C, 50 h; r.t., 96 h).

Scheme 39

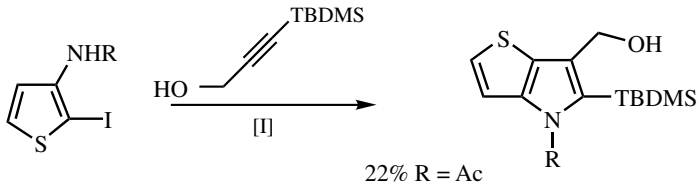


Scheme 40



[I] 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, KOAc or K_2CO_3, MeCN or anisole, 60 or 130 °C, 15–24 h; [II] 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, Et_4NCl, K_2CO_3, MeCN, rfx, 3–3.5 h; [III] 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, Et_4NCl, K_2CO_3, MeCN, rfx, 17 h; [IV] 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, TlOAc, Et_4NCl, MeCN, rfx, 15 h; or DMF, 100 °C, 9 h.

Scheme 40 (*Continued*)



99

[I] 5 mol % $Pd(OAc)_2$, $(n\text{-}Bu)_4NCl$, 90–100 °C, Na_2CO_3, or KOAc, 3–22 h.

Scheme 41

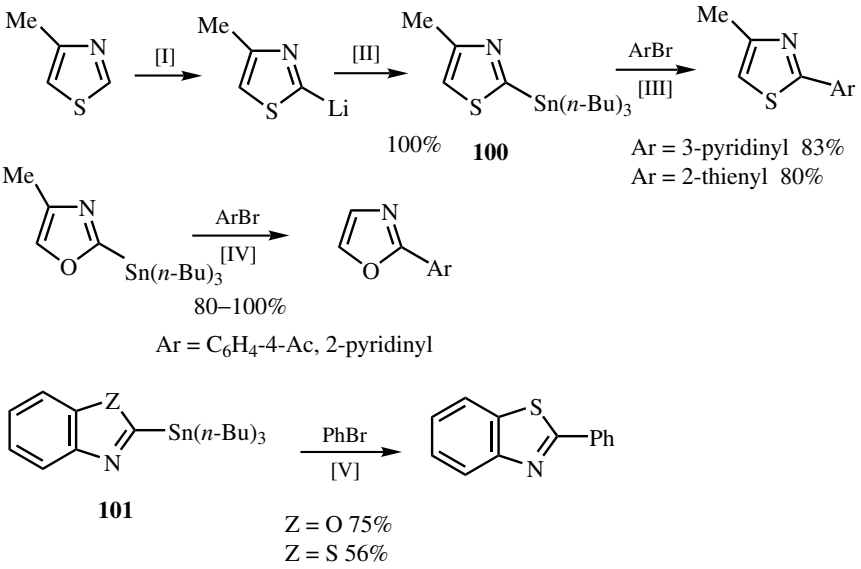
C. CROSS-COUPLING IN AZOLES

C.i. Metallated Azoles

C.i.a. *Arylation*

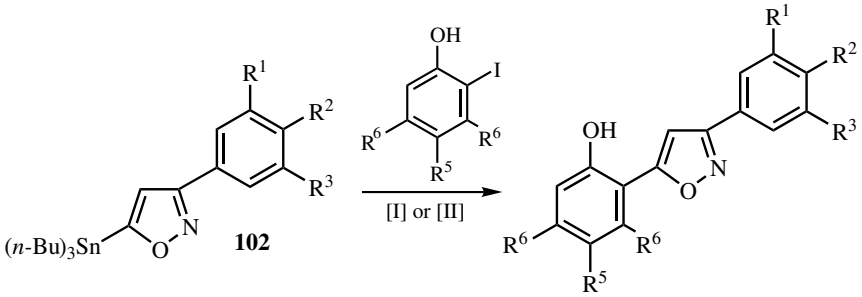
Tin Derivatives A convenient and direct method for the preparation of metallated species in the azole series starts with lithiation, as in the case of π-excessive systems. In thiazoles the initial lithiation is in the 2-position. Subsequent quenching with a stannyl halide will furnish a stannane substrate **100** to be used for Stille couplings with aryl or heteroaryl halides, in the present case with a bromide[7] (**Scheme 42**). Stannylated oxazoles are similarly prepared and react in the same manner.[58] The same applies to their benzannulated analogs **101**.[59]

Isoxazoles are initially metallated in the 5-position. The 5-stannyl derivatives **102** (**Scheme 43**) could be cross-coupled with hydroxy- and methoxy-substituted 2-iodophenols

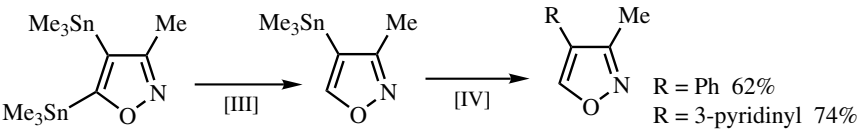


[I] *n*-BuLi, THF-hexane, –80 to –65 °C, 15 min; [II] $(n\text{-Bu})_3SnCl$, THF, –70 °C, 15 min; [III] 2 mol % $Pd(PPh_3)_4$, benzene, DMF, rfx, 5 h; [IV] 5 mol % $Pd(PPh_3)_4$, benzene, rfx, 12–24 h; [V] 1 mol % $Cl_2Pd(PPh_3)_2$, xylene, 120 °C, 20 h.

Scheme 42



R^1, R^2, R^3, R^4, R^5, R^6 = H, OH, OMe [I] 35–81%
R^1, R^3, R^4, R^5, R^6 = H, R^2 = OH [II] 95%
R^1, R^3, R^4, R^5 = H, R^2, R^6 = OH [II] 78%



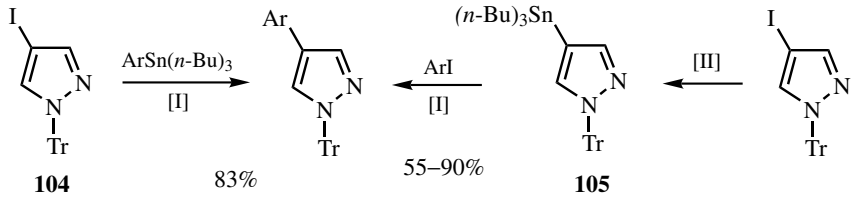
103

[I] 5 mol % $PdCl_2$, dioxane, rfx, 5 h; [II] 5 mol % $Pd_2(dba)_3$, 20 mol % $AsPh_3$, dioxane, 45 °C, 48 h; [III] NH_4OH, EtOH-H_2O, 150 °C, 15 h; [IV] 2–5 mol % $Cl_2Pd(PPh_3)_2$, dioxane, rfx, 24–36 h (PhCO, 3 h).

Scheme 43

to yield 3-aryl-5-(2-hydroxyaryl)isoxazoles. Triphenylphosphine was the preferred ligand except when the substrates were rich in hydroxy groups, in which case triphenylarsine as ligand gave the higher yields of the coupling product.[60] 4-Stannylisoxazoles **103** can be prepared by a 1,3-dipolar cycloaddition reaction of bis(tributylstannyl)acetylene with nitrile oxides, followed by treatment with aqueous ammonia in ethanol in a sealed tube to remove selectively the stannyl group at the more acidic 5-position. The product in the present case is 4-(*n*-tributyl)stannyl-3-methylisoxazole. Pd-catalyzed cross-coupling with iodobenzene or 3-bromopyridine leads to the corresponding aryl- and heteroaryl-substituted derivative.[61]

N-Trityl-4-iodopyrazole **104** can be coupled with stannylbenzenes using PdC/CuI/$AsPh_3$ as the catalyst system (**Scheme 44**). The 4-anisylstannane gave the coupling product in good yield. Lower yields were obtained from the 4-phenol and 4-anilino analogs, and the reaction failed for the 4-nitro derivative. Better results were obtained when the polarization of the reactants was reversed, that is, in the coupling between 4-stannylpyrazoles **105** and phenyl iodides. The stannyl substrate is available from 4-halogenopyrazole by lithiation with *t*-butyllithium and subsequent treatment with the stannyl chloride.[62]



Ar = C_6H_4-4-OMe 79%

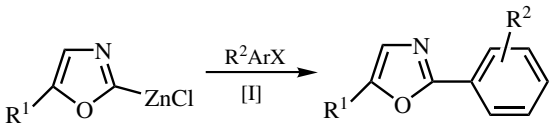
Ar = C_6H_4-4-OH, 4-NH_2 11–27%

[I] 1.3 mol % Pd-C (10%), $AsPh_3$, CuI, MeCN, rfx, 48 h;
[II] (i) *t*-BuLi, THF-Et_2O, −78 °C, (ii) $(n\text{-Bu})_3SnCl$.

Scheme 44

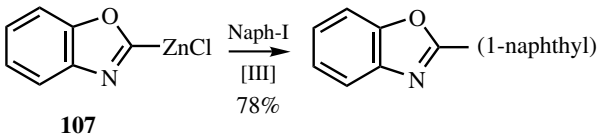
Zinc Derivatives Oxazoles and benzoxazoles can be lithiated in the 2-position by alkyllithium. In transmetallation of lithiated oxazole excess zinc dichloride gave the highest yield. The zincated substrates **106** and **107** were used in Negishi-type coupling (**Scheme 45**). Reactions of zincated oxazoles and benzoxazole with aryl halides all proceed well.[63] A similar reaction sequence was used in the preparation of a 2-oxazolyl-substituted tricyclic structure **108**.[64]

1,2,3-Triazoles are lithiated next to the *N*-substituted nitrogen **109** by analogy to metallation in *N*-substituted pyrrole and pyrazole (**Scheme 46**). Alternatively, directed *ortho*-metallation (DOM) can be used to explain metallation in the 5-position. Zincation is effected by quenching with zinc iodide. Stannylation is effected similarly with a stannyl chloride. The zincated substrate readily undergoes the Negishi reaction with aryl iodides. The cross-coupling was less effective with stannanes as substrates. In the case of 2-fluoro-1-iodobenzene, the coupling reaction proceeded more readily than for the corresponding bromide and chloride. In general, iodo derivatives of the heterocycle reagent were used in the heteroarylation.[65]

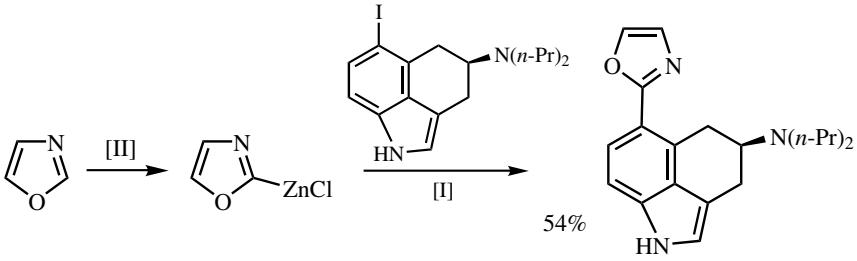


106

R^1 = H, Ph, R^2 = C_6H_4-4-Ac, 2-Me, 4-OMe, 4-NO_2

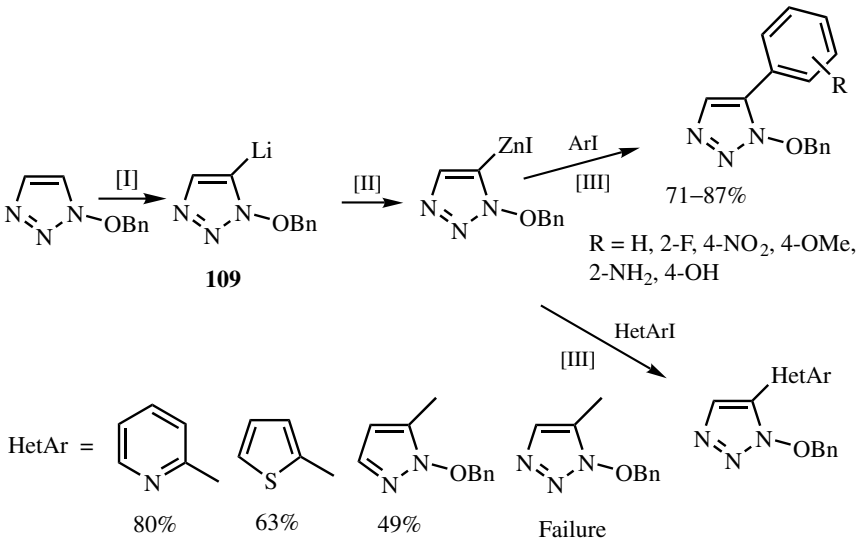


107



[I] (i) 5 mol % $Cl_2Pd(PPh_3)_2$, 10 mol % *n*-BuLi, THF, rfx, 1–2 h; **108**
[II] (i) *n*-BuLi, −70 °C, THF, (ii) $ZnCl_2$, Et_2O, −78 °C to r.t.

Scheme 45



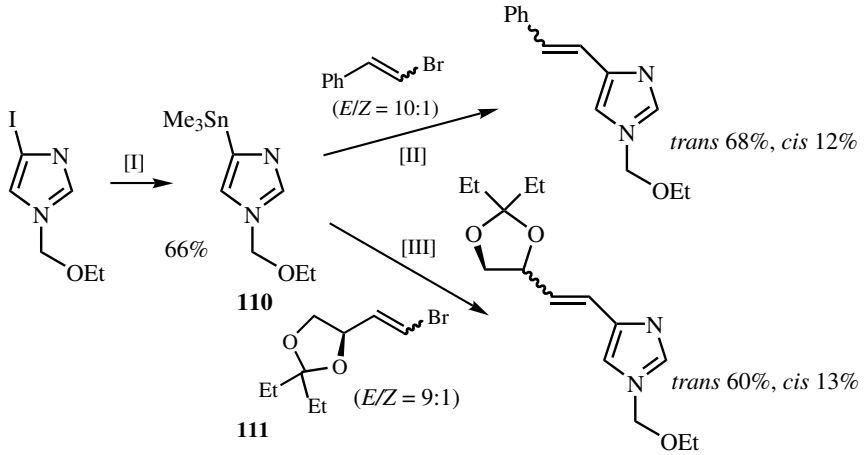
109

[I] *n*-BuLi, THF, −78 °C; [II] ZnI_2; [III] 2–5 mol % $Pd(PPh_3)_4$, THF, −78 °C to r.t., 30 min.

Scheme 46

C.i.b. *Alkenylation*

Tin Derivatives Treatment of *N*-protected 4-iodoimidazole with ethylmagnesium bromide in anhydrous dichloromethane followed by quenching with trimethyltin chloride will give the 4-stannylated imidazole **110** (**Scheme 47**). Subsequent Stille coupling has been effected with β-bromostyrene or the bromovinyl-dioxole **111**.[66]



[I] (i) EtMgBr, CH_2Cl_2-Et_2O, r.t., 30 min; (ii) Me_3SnCl, 0 °C to r.t., 2 h; [II] 5 mol % $Pd_2(dba)_3$, 10 mol % $AsPh_3$, 10 mol % CuI, DMF, 80 °C, 3 h; [III] 5 mol % $Cl_2Pd(PPh_3)_2$, DMF, 80 °C, 8 h.

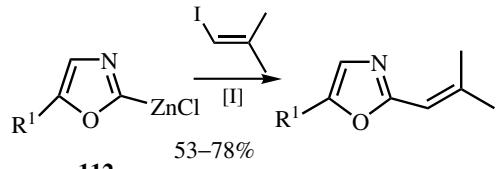
Scheme 47

Zinc Derivatives Oxazole and 5-substituted oxazoles are lithiated in the 2-position. Subsequent zincation gives the corresponding 2-oxazolylzinc chloride **112** for alkenylation (**Scheme 48**). Excess of zinc chloride was used in the zincation. Subsequent cross-coupling with a 1-butenyl iodide yields 2-alkenyl derivatives. The Pd-catalyst was pregenerated by reduction with DIBALH.[67] The alkenylated oxazole **113** was formed in a corresponding coupling reaction with a cyclic vinyl triflate.[63]

C.i.c. *Carbonylation and Acylation*

Tin Derivatives. 5-Stannylated or 5-zincated 1-benzyloxy-1,2,3-triazole, **114** and **115**, respectively, is available from the 5-lithiated species by quenching with the respective metal halide (**Scheme 49**). Either metal complex is a good substrate for ketone formation **116** in the 5-position with acid chloride reagents.[65]

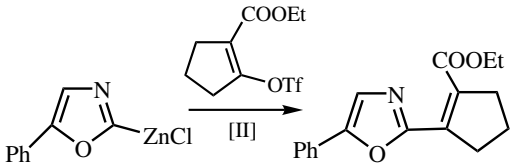
C.i.d. Heck Reaction. π-Deficient chloropyrazines can be Heck-coupled into 1,3-azoles (**Scheme 50**). It will be recalled that the same methodology was used to couple into the π-excessive furan, thiophene, and pyrrole heterocycles and their benzo derivatives (*vide supra*). The Heck reaction in oxazole and thiazole proceeds in a regiospecific manner. The new carbon–carbon bond is formed in the 5-position **117** next to the "ether" heteroatom as commonly observed in vinyl ethers and strongly favored in furan and thiophene. In benzoxazole and benzothiazole the only vacant position is between the two heteroatoms, and the Heck coupling results in substitution into the 2-position **118**.[45]



53–78%

112

R^1 = H, Ph, 3-methylisoxazol-5-yl

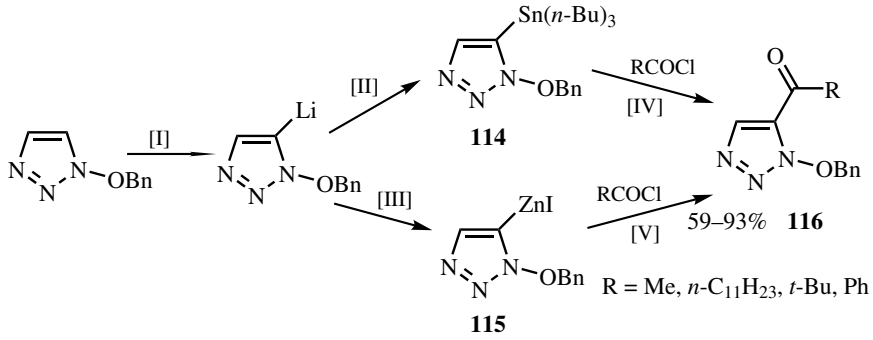


84%

113

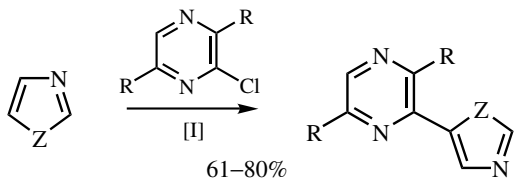
[I] (i) 10 mol % $Cl_2Pd(PPh_3)_2$, 20 mol % DIBALH, THF, (ii) r.t., 1–6 h;
[II] (i) 5 mol % $Cl_2Pd(PPh_3)_2$, 10 mol % *n*-BuLi, THF, (ii) rfx, 1–2 h.

Scheme 48



[I] *n*-BuLi, THF, −78 °C; [II] $(n\text{-Bu})_3SnCl$; [III] ZnI_2; [IV] 2–5 mol % $Pd(PPh_3)_4$, THF, − 78 °C to r.t., 30 min; [V] as [IV] except for 2 h reaction time.

Scheme 49

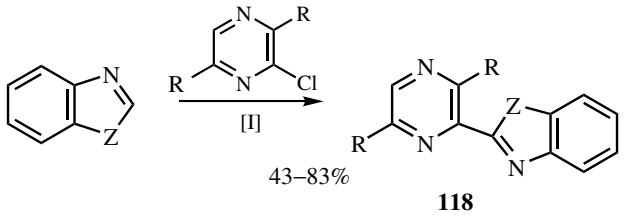


61–80%

117

R = Me, Et, *iso*-Bu Z = O, S

Scheme 50



118

R = Me, Et, *i*-Bu Z = O, S

[I] 5 mol % $Pd(PPh_3)_4$, AcOK, DMA, rfx, 6 h.

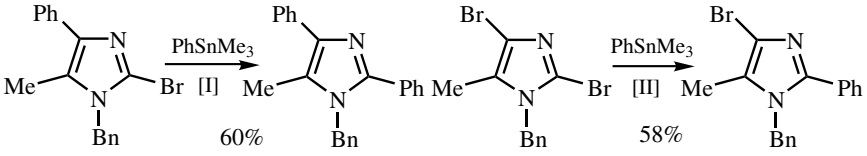
Scheme 50 (*Continued*)

C.ii. Halogeno- or Triflyloxy-Substituted Azoles

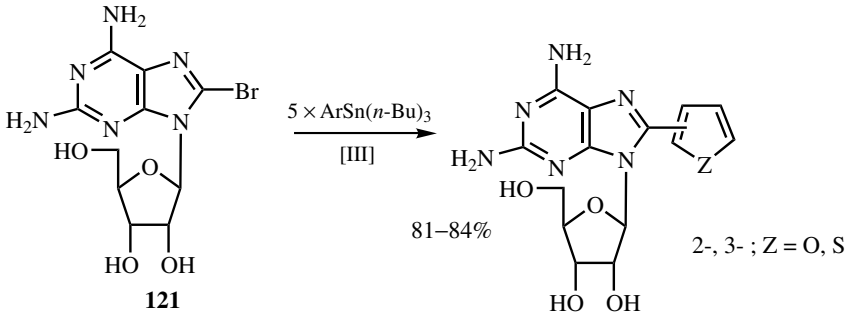
C.ii.a. *Arylation*

Tin Reagents. Stille coupling in the 2-position in the 2-bromoimidazole **119** gives the 2-phenyl derivative (**Scheme 51**). In the 2,4-dibromoimidazole **120** regioselective monocoupling in the more electrophilic 2-position gives the 2-phenylated product. A stepwise coupling would allow for differential substitution in 2,4-dibromoimidazoles.[68] Stille coupling between trimethylsilyl-protected 9-(*β-D*-ribofuranosyl)-2,6-diamino-8-bromopurine **121** and 2- or 3-tri(*n*-butyl)stannylthiophene proceeds well. Similar couplings are effected with 2- or 3-tri(*n*-butyl)stannylfuran. The catalyst system was Cl_2Pd(dppp) with cupric oxide as cocatalyst. Excess of the 2- and 3-tri(*n*-butyl)stannylthiophene and -furan reagents had to be used.[69] 4-Substituted 3-halogeno- and 3-triflyloxy-1,2,5-thiadiazoles **122** can be arylated in reactions with appropriate stannanes. In reactions of 1,2,5-thiadiazoles with organometallic reagents, Grignard reagents, and alkyllithium reagents, reductive cleavage of a nitrogen–sulfur bond to form ring-opened products is a complicating factor. This is avoided in Pd-mediated carbosubstitution reactions. 1,2,5-Thiadiazole is a π-deficient heterocycle. In many cases coupling can therefore be effected with a chloro substituent in the electrophilic 3-position **122**. In this case, however, the bromo derivative was the more active. Triflates are highly reactive when the reaction is carried out in the presence of lithium chloride.[70] The bromide **123** is a useful substrate for the coupling of aryl- and heteroarylstannanes into the 5-position in 3-amino-4-arylisothiazole 1,1-dioxides. In general, the best results were obtained using benzyl chlorobis(triphenylphosphine)palladium as catalyst.[71]

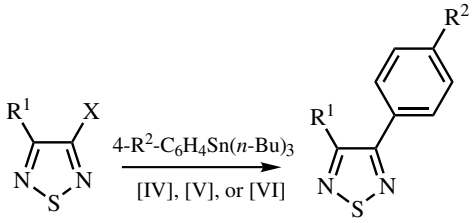
Boron Derivatives. A 5-substituted imidazole can be selectively brominated in the 4-position (**Scheme 52**). Suzuki coupling conditions for the 4-bromo imidazole with phenylboronic acid gives the 4-phenylimidazole **124**.[68] 2-Bromothiazole reacts similarly with phenylboronic acid carrying an *o*-carbamoyl group **125**.[72] The Suzuki type coupling between 6-substituted 1-benzyl-2-iodo-1*H*-benzimidazoles **126** and aryl boronic acids can be used for the preparation of the corresponding 2-aryl-1*H*-benzimidazoles **127**. The reaction series is initiated by regioselective lithiation in the 2-position. Subsequent treatment with NIS furnished the 2-iodo derivative. Phenylboronic acids, substituted in the *ortho* positions, required more vigorous reaction conditions than those substituted elsewhere.[73]



119 **120**

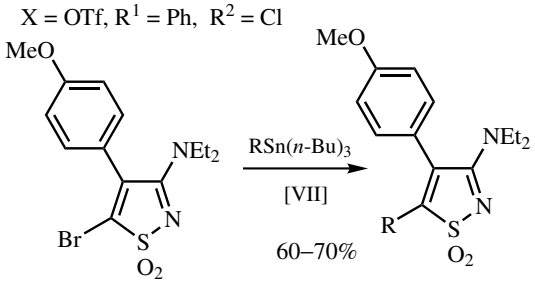


121



122

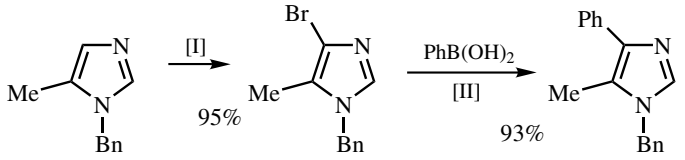
[IV] 51–92% X = Br, R^1 = Ph, 2,6-$Cl_2C_6H_3$, *tert*-Bu, R^2 = H, Cl, MeO, Me; [V] 90% X = Br, R^1 = Ph, R^2 = Cl; [VI] 83% X = OTf, R^1 = Ph, R^2 = Cl



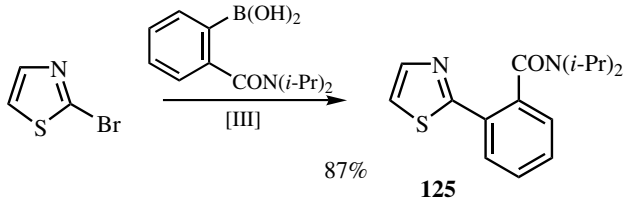
123 R = Ph, 2-pyridinyl, 3-(1-ethoxycarbonyl)indolyl

[I] 2 mol % $Cl_2Pd(PPh_3)_2$, toluene, rfx, 12 h; [II] 10 mol % $Cl_2Pd(PPh_3)_2$, toluene, rfx, 12 h; [III] (i) HMDS, pyridine, $(NH_4)_2SO_4$, (ii) Cl_2Pd(dppb), CuO, DMF, 110 °C, 2–3.5 h; [IV] 5 mol % $Pd(PPh_3)_4$, toluene, 120 °C, 12 h; [V] 5 mol % $Cl_2Pd(PPh_3)_2$, toluene, 120 °C, 12 h; [VI] 5 mol % $Pd(PPh_3)_4$, LiCl, toluene, 120 °C, 12 h; [VII] 10 mol % $PhCH_2ClPd(PPh_3)_2$, toluene, rfx, 1 h.

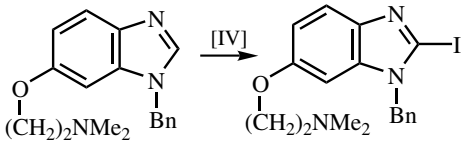
Scheme 51



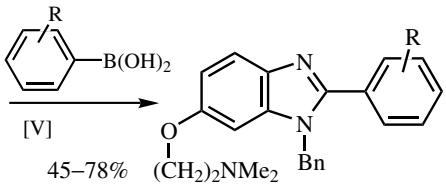
124



125



126



127

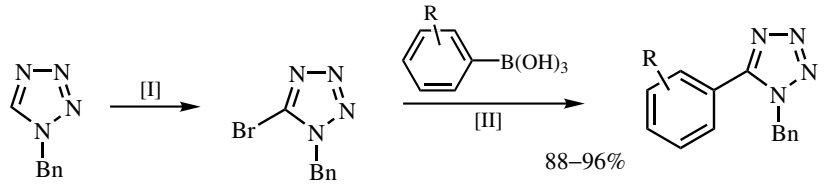
R = 4-Me, 3,5-*t*-Bu_2, 3,5-Ph_2, and 2-naphthyl

[I] NBS, MeCN; [II] 5 mol % $Pd(PPh_3)_4$, Na_2CO_3, toluene, dil EtOH, rfx, 24 h; [III] 3 mol % $Pd(PPh_3)_4$, aq. Na_2CO_3, toluene, rfx, 6 h; [IV] (i) *n*-BuLi, THF, −78 °C, (ii) NIS; [V] 5 mol % $Pd(PPh_3)_4$, Na_2CO_3, toluene-EtOH (20:1), rfx, 24 h.

Scheme 52

Bromination in *N*-benzyltetrazole can be effected by initial lithiation in the 5-position follwed by addition of bromine (**Scheme 53**). The bromo substrate **128** can be phenylated by coupling with phenyl(tri-*n*-butyl)stannane for the preparation of the 5-phenyl derivative. A better process, however, was to carry out the coupling with phenylboronic acids under Suzuki conditions.[74]

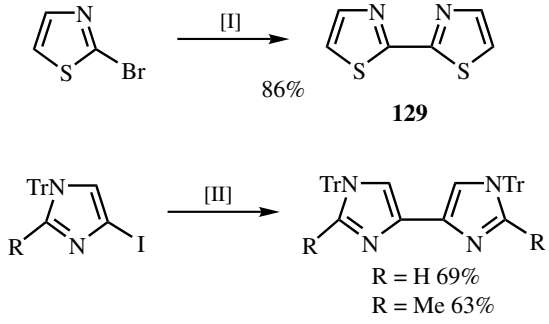
Homocoupling. Homocoupling of heteroarenes leads to symmetrical coupling products as described for thiophenes (*vide supra*). The catalyst system can be generated from palladium diacetate and an amine base. 2-Bromothiazole is converted to the 2,2'-biheteroarene **129** in high yield under these conditions (**Scheme 54**).[35] Similarly, *N*-tritylated 4-iodoimidazoles can be homocoupled to give 4,4´-bis(imidazoles).[75]



128 R = H, 4-Me, 4-F, 4-OMe, 2-OMe, 2-CH_2OBn, 2-$CON(i\text{-}Pr)_2$

[I] (i) *n*-BuLi, THF, −78 °C, (ii) Br_2; [II] 3 mol % $Pd(PPh_3)_4$, Na_2CO_3, toluene-H_2O-EtOH (8:1:1), 110 °C, 20 h.

Scheme 53



129

[I] 5 mol % $Pd(OAc)_2$, $NEt(i\text{-}Pr)_2$,$(n\text{-}Bu)_4NBr$, toluene, 105 °C, 23 h;
[II] 5 mol % $Pd(PPh_3)_4$,NEt_3, DMF, 110 °C, 24−48 h.

Scheme 54

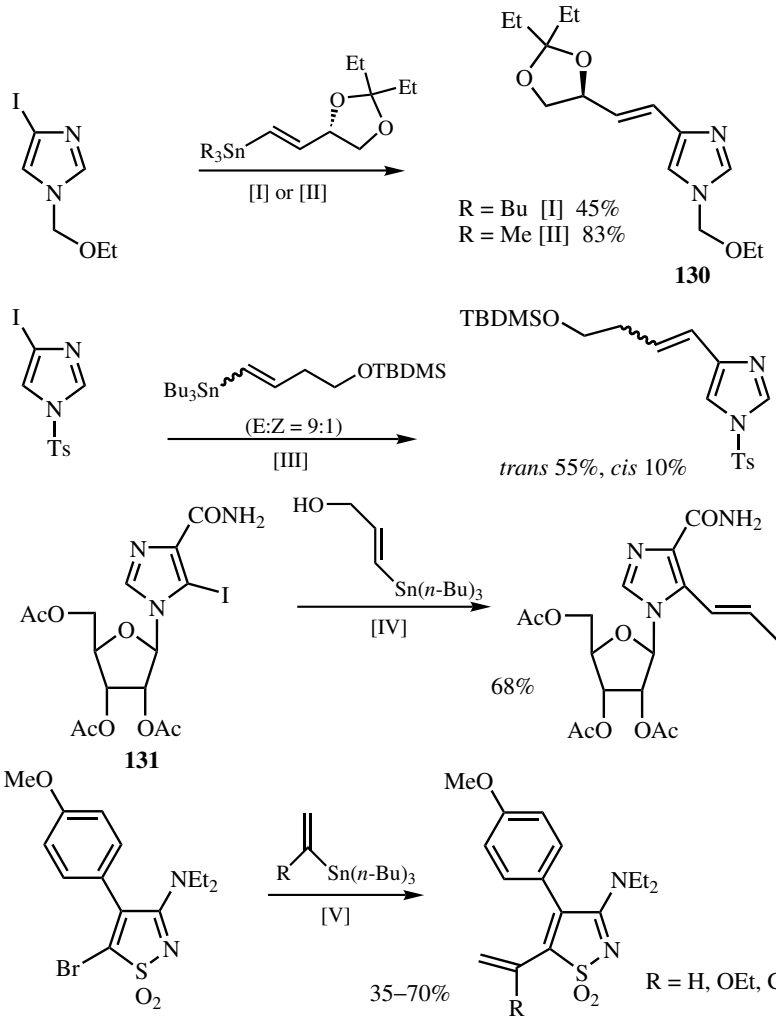
C.ii.b. *Alkenylation*

Tin Reagents. Vinyltrialkyltin reagents can be used for introduction of alkenyl substituents into the 4-position in *N*-protected imidazoles **130** (**Scheme 55**). In this particular case alkenylation reaction under Heck conditions was unsatisfactory due to facile homocoupling of the heterocycle.[66] A related series of reactions has been used for introduction of an allylic alcohol substituent into the imidazole 4-position in a ribosylimidazole nucleoside **131**.[76] Vinylation of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide **132** with vinylstannane reagents can be used for the preparation of 5-alkenylated isothiazole 1,1-dioxides.[71]

Boron Reagents. Tetrazole can be lithiated in the 5-position and brominated to yield a 5-bromo substrate that reacts with a vinylboronic acid to furnish the corresponding vinyltetrazole **133** (**Scheme 56**).[74]

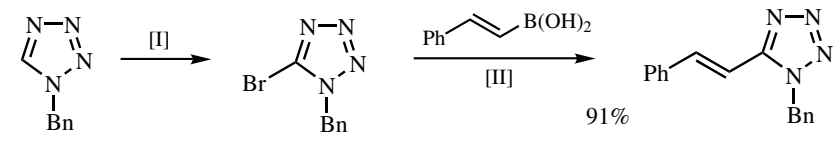
C.ii.c. *Alkynylation*

Copper Reactants. 4-Alkynyl imidazoles are available from *N*-protected 4-iodoimidazoles and alkynes or alkynyltrialkyltin derivatives (**Scheme 57**). Reactions under Sonogashira conditions can be used to prepare the cross-coupled products **134**. The same



[I] 5 mol % $Pd_2(dba)_3$, 10 mol % $AsPh_3$, 10 mol % CuI, DMF, 80 °C, 24 h; [II] 5 mol % $Pd(PPh_3)_4$, DMF, 80 °C, 24 h; [III] 5 mol % $Pd_2(dba)_3$, 10 mol % $AsPh_3$, 10 mol % CuI, DMF, 80 °C, 3 h; [IV] 10 mol % $Cl_2Pd(PhCN)_2$, MeCN, 100 °C, 12 h; [V] 10 mol % $PhCH_2ClPd(PPh_3)_2$, toluene, rfx, 0.25–4 h.

Scheme 55



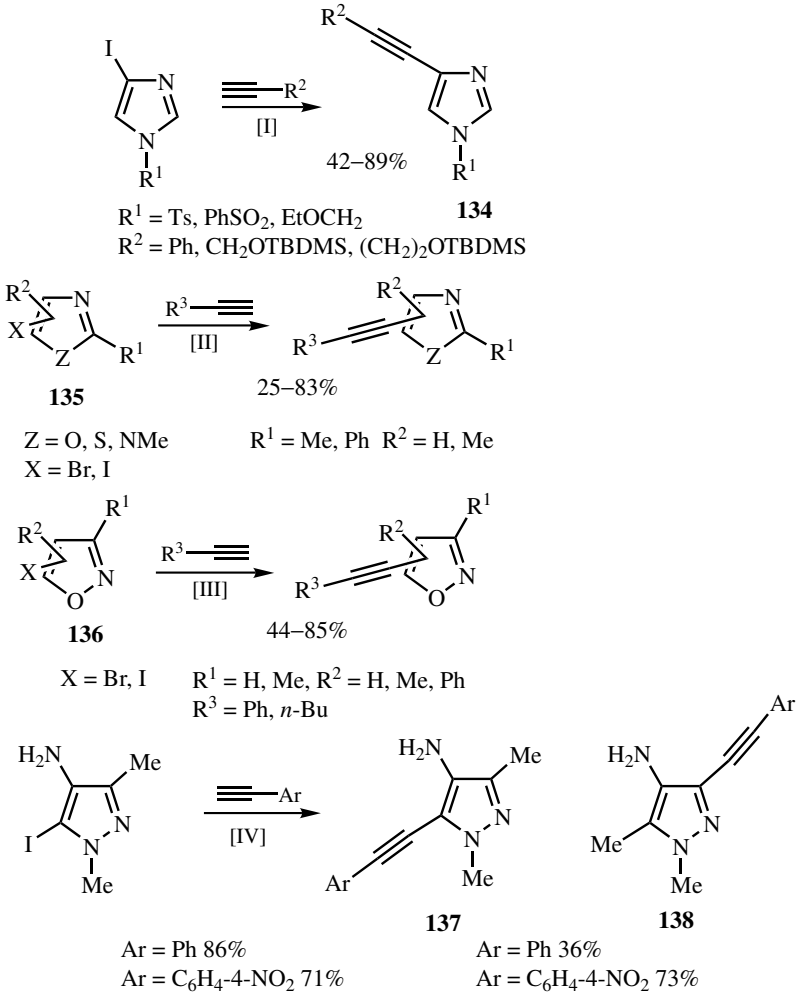
[I] (i) *n*-BuLi, THF, −78 °C; (ii) Br_2; [II] 3 mol % $Pd(PPh_3)_4$, Na_2CO_3, toluene-H_2O-EtOH (8:1:1), 110 °C, 20 h.

Scheme 56

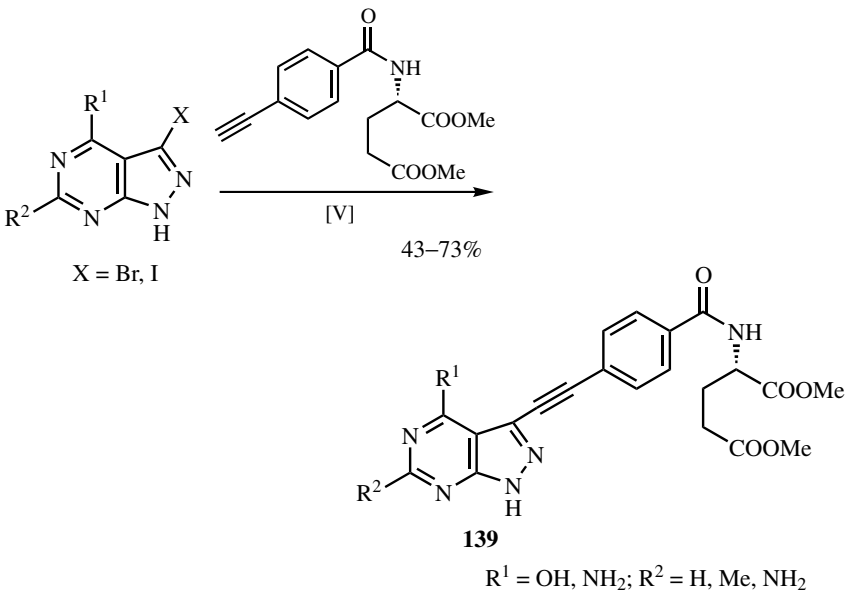
products were formed under Stille conditions using alkynylstannanes for the coupling reaction.[66] A number of 4- and 5-bromo- and iodo-oxazoles, -thiazoles, and *N*-methylimidazoles **135** have been alkynylated under Sonogashira conditions. Alkynylation reactions in the 2-position were less successful.[77] Isoxazoles **136** have been alkynylated in a similar manner.[78] Aminopyrazoles react similarly to furnish the alkynylated products **137** and **138**.[79] The same methodology has been applied for the preparation of pyrazolo[3,4-*d*]pyrimidine derivatives **139** by coupling of the 3-iodo or 3-bromo heterocycle with dimethyl 4-ethynylbenzoyl-*L*-glutamate.[80]

C.ii.d. *Alkylation*

Sodium Salts of Stabilized Carbanions. The carbosubstitution in 4- and 5-bromo-2,4- or 5,6-diphenyl-1,3-azoles **140** (oxazoles, thiazoles, and imidazoles) with phenylsulfonylacetonitrile in the presence of a strong base is promoted by palladium catalysis



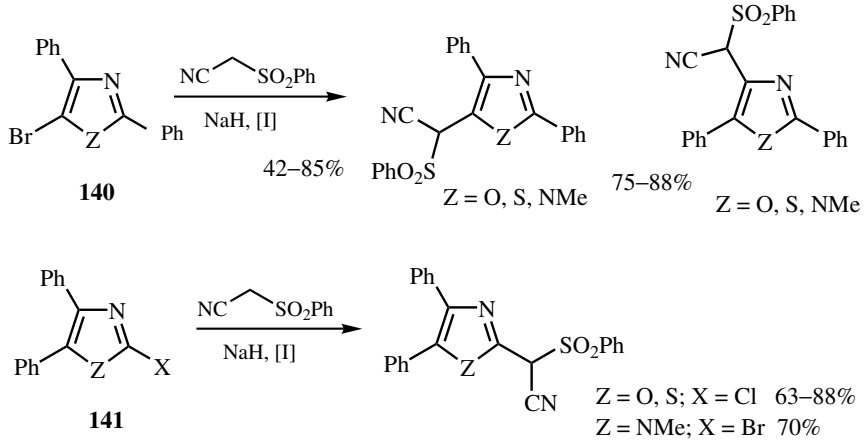
Scheme 57



[I] 5 mol % $Pd(PPh_3)_4$, 10 mol % CuI, Et_3N, DMF, 80 °C, 3 h; [II] 4 mol % $Cl_2Pd(PPh_3)_2$, CuI, Et_3N, 80–100 °C, 3–15 h; [III] 2 mol % $Cl_2Pd_2(PPh_3)_2$, PPh_3, CuI, NEt_3, rfx, 10–124 h; [IV] 1.2 mol % $Cl_2Pd(PPh_3)_2$, CuI, Et_3N, 80 °C, 0.5–8 h; [V] 8 mol % $Pd(PPh_3)_4$, CuI, NEt_3, DMF, 85–105 °C, 3–18 h.

Scheme 57 (*Continued*)

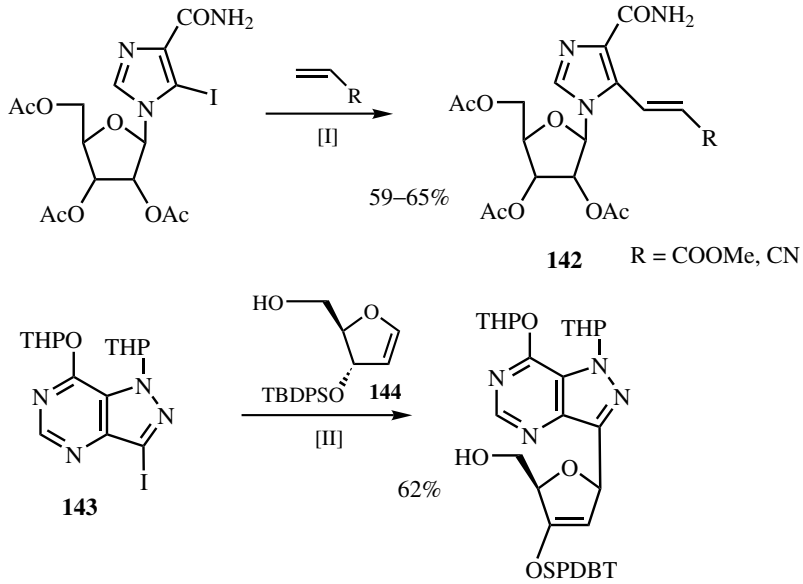
(**Scheme 58**). 2-Chloro-oxazole or -thiazole substrates **141** were used for substitution in the electrophilic 2-position. The 2-chloro-*N*-methylimidazole, however, showed low reactivity, and therefore the iodo analog was used in the coupling. A similar series of reactions was run for carbosubstitution in the 4-position in 1,2-azoles.[81]



[I] 4 mol % $Pd(PPh_3)_4$, $(MeOCH_2)_2$, rfx, 1.5–24 h.

Scheme 58

C.ii.e. ***Heck Reaction*** The cross-coupling between 5-iodoimidazoles and methyl acrylate has been applied to complex structures as depicted for the preparation of (*E*)-5-(2-carbomethoxyvinyl)-1-(2,3,5-tri-*O*-acetyl-*beta*-*D*-ribofuranosyl)imidazole-4-carboxamide **142** from the corresponding 5-iodoimidazole (**Scheme 59**). Acrylonitrile reacts in the same manner under Heck conditions to provide the (*E*)-5-cyanovinyl derivative.[76] The *C*-glycosyl bond formation in the Heck coupling between the 3-iodopyrazolo[4,3-*d*]pyrimidine **143** and the ribofuranoid glycal **144** was regio- and stereospecific. The iodo substituent in the substrate was introduced by a simple electrophilic substitution.[82]



[I] 10 mol % $Cl_2Pd(PhCN)_2$, NEt_3, MeCN 100 °C; [II] 10 mol % Pd(dba), 20 mol % $AsPh_3$, $N(n\text{-}Bu)_3$, MeCN, 80 °C, 20 h.

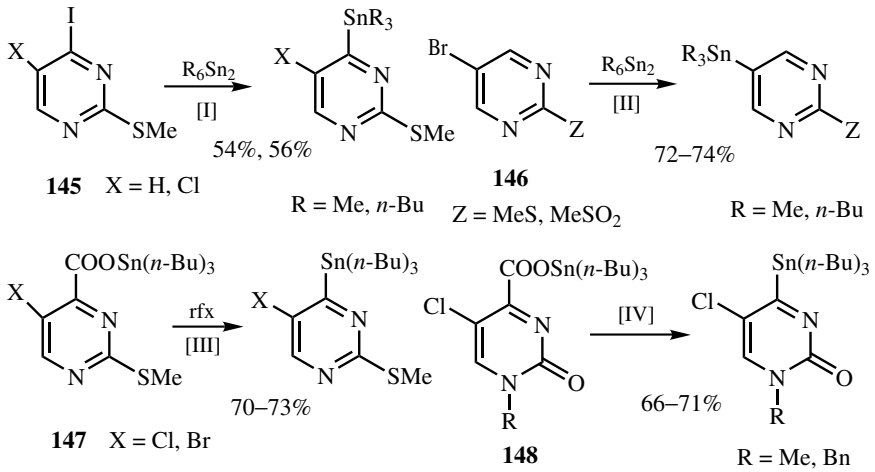
Scheme 59

CROSS-COUPLING IN π-DEFICIENT RING SYSTEMS

D.i. Metallated Six-Membered Ring Systems

D.i.a. *Arylation*

Tin Derivatives. Most stannanes are stable compounds that can be isolated and purified in the normal manner for organic compounds. Generally, stannylation is effected by a transmetallation reaction between an organostannyl chloride and a lithiated species. This method works well in the benzenoid position in pyrimidines. Stannylation in the 4-position can be effected on 4-iodo derivatives **145** (**Scheme 60**) using hexaalkyldistannanes in the presence of fluoride ions.[83] The same product is obtained when the stannylation is effected by tri(*n*-butyl)stannylcopper in THF at −78 °C. Bis(π-allyl)palladium chloride is the recommended catalyst for the coupling of 5-bromopyrimidines **146** with hexaalkyldistannanes to form 5-stannanes. The presence of halide ions promotes the reaction, especially fluoride ions.[84] The promoting effect is ascribed to the high affinity of fluoride ions for tin. Stannylation in the 5-position can also be effected by a



[I] 3 mol % $(AcO)_2Pd(PPh_3)_2$, $(n\text{-}Bu)_4NF$, THF, r.t., 6 h; [II] 3 mol % $Cl_2Pd_2(\pi\text{-allyl})_2$, $(n\text{-}Bu)_4NF$, THF, rfx, 9 h; [III] 3 mol % $Cl_2Pd(MeCN)_2$, anisole, rfx, 4–6 h; [IV] anisole, rfx, 45 min.

Scheme 60

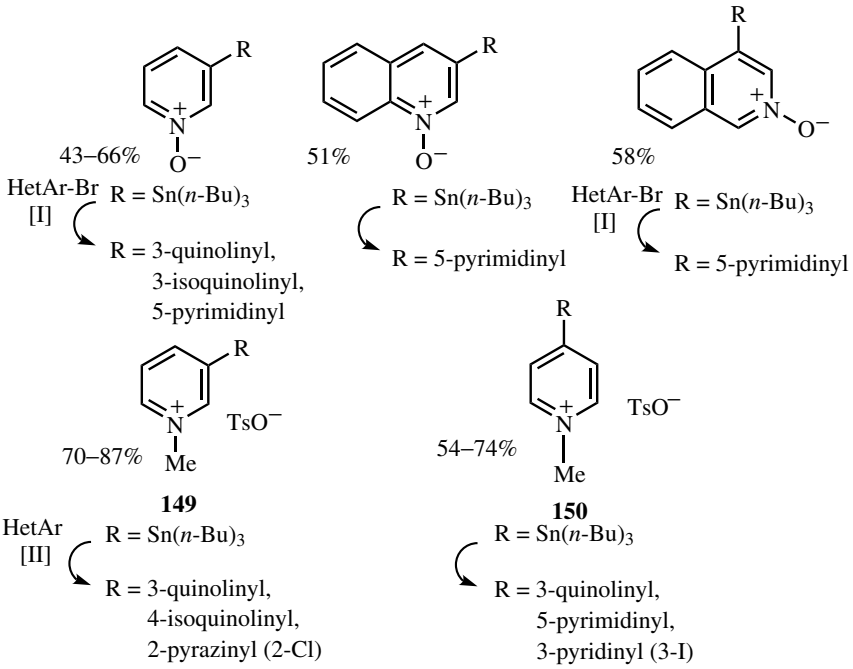
metal–metal exchange with trialkylstannylcopper or -sodium reagents. Thermal decarboxylation of a stannyl carboxylate **147** can be used for stannylation in the electrophilic 4-position. The reaction is promoted by Pd catalysis.[83] In the more π-electron-deficient 2-pyrimidinone carboxylic ester **148**, decarboxylation with concurrent stannylation in the 4-position takes place without palladium catalysis.

Stannylated azines have been widely used for cross-coupling. *N*-Oxides of tri(*n*-butyl)stannylated pyridine, quinoline, and isoquinoline and tri(*n*-butyl)stannylated *N*-methiodides of pyridine and quinoline have been coupled with heteroaryl halides (**Scheme 61**). The use of tosylate as a counterion for the quaternized salts **149** and **150** minimized decomposition of the stannane whereas iodide anion promotes destannylation.[85]

The yield of coupling products from 5-stannylated pyrimidines **151** is normally high (**Scheme 62**).[84] Pyrimidines with the stannyl group in the electrophilic 4-position **152** also react well.[83] Carbosubstitution in the 4-position in the 2-pyrimidinone **153** proceeds under similar conditions. In the pyridine series, the coupling reaction is exemplified by the reaction of a 4-stannyl derivative with a triflate of a benzonaphthyridine for the preparation of a pyridinylbenzonaphthyridine **154**.[86]

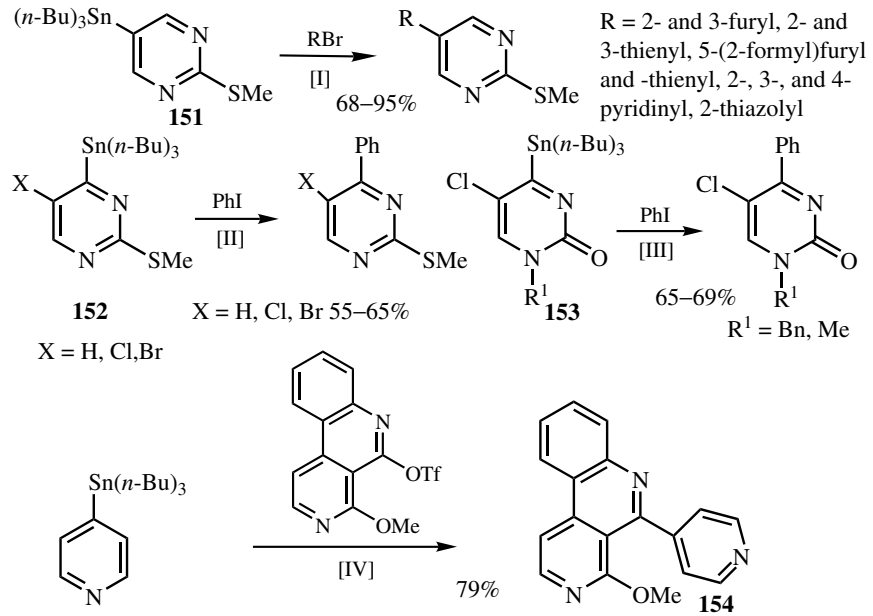
Zinc Derivatives. Zincated and *N*-protected 6-iodouracil **155** can be used under Negishi conditions for the preparation of 6-arylated uracil derivatives (**Scheme 63**). The conversion of the 6-iodouracil derivative is best performed using highly active zinc dust in DMAC.[87] The oxidative addition of active zinc has also been applied to a number of other iodo- and bromo-substituted π-deficient heteroarenes such as pyridine, pyrimidine, and quinoline, giving the corresponding heteroarylzinc halides **156**, which are transformed to arylated derivatives by palladium catalysis.[88]

Magnesium Derivatives. Iodopyridines undergo iodine–magnesium exchange when treated with alkyl- or phenylmagnesium halides. The more readily available bromo- and



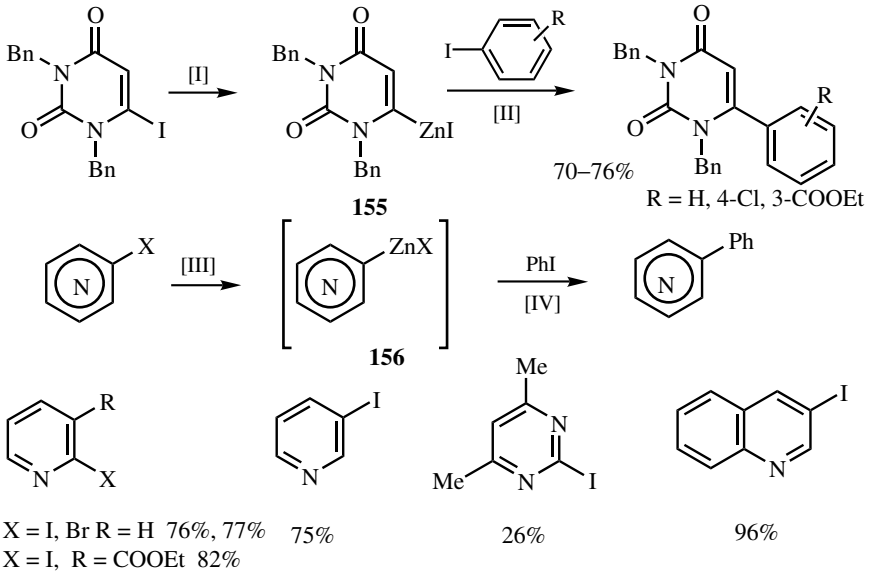
[I] 10 mol % $Pd(PPh_3)_4$, THF or DMF, rfx, 12 –24 h; [II] 10 mol % $Cl_2Pd(dppe)_2$, toluene, rfx, 20–30 h.

Scheme 61



[I] 3 mol % $Cl_2Pd(PPh_3)_2$, THF, DCE or DMF, 80 °C, to-rfx, 5–24 h; r.t., 6 h; [II] 3 mol % $Cl_2Pd(PPh_3)_2$, DCE, rfx, 4 h; [III] 3 mol % $Cl_2Pd(MeCN)_2$, DCE, rfx, 5 h; [IV] 3 mol % $Pd(PPh_3)_4$, LiCl, dioxane, rfx, 36 h.

Scheme 62

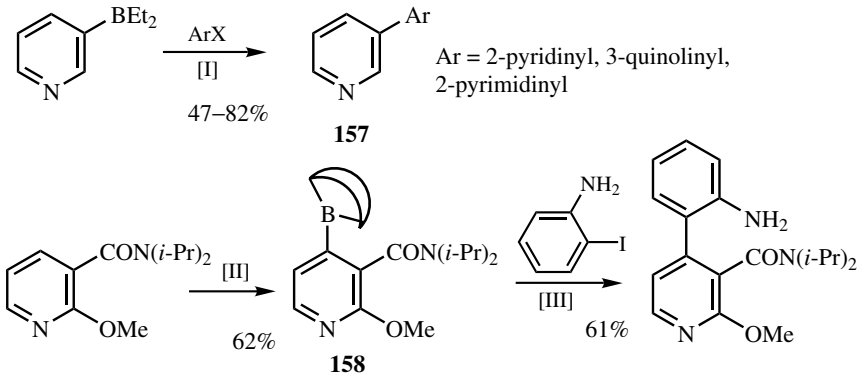


[I] Zn, DMAC, 25 °C, 1 h; [II] 1 mol % $Pd(dba)_2$, 4 mol % $P(2\text{-furyl})_3$, DMAC, 0 °C to r.t., 4 h; [III] Zn*, THF, r.t., 1.5–6 h; [VI] 0.5 mol % $Pd(PPh_3)_4$, THF, r.t., 41–47 h.

Scheme 63

chloropyridines are converted into corresponding magnesium chlorides when treated with isopropylmagnesium chloride in THF at room temperature.[89] By analogy to the findings in the five-membered heterocyclic series, azine magnesium halides are expected to become useful substrates for cross-coupling reactions.

Boron Derivatives. Coupling of diethyl(3-pyridinyl)borane with 2-chloropyridine, 2-chloropyrimidine, and 3-bromoquinoline under Suzuki conditions gives the corresponding 3-heteroarylpyridine **157** (**Scheme 64**).[34] The 4-pyridinylborane **158** can be prepared by



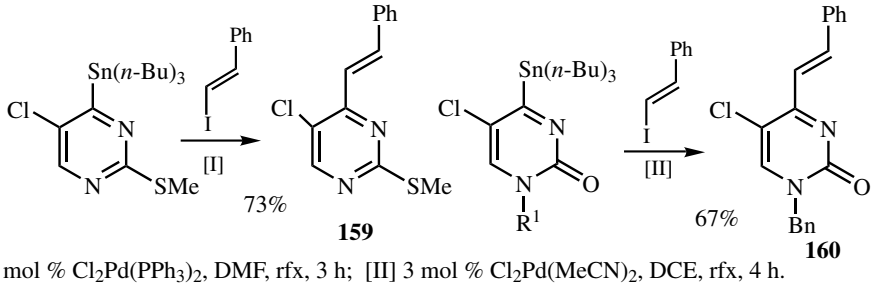
[I] 5 mol % $Pd(PPh_3)_4$, THF, KOH, (n-$Bu)_4NBr$, rfx, 8 h; [II] (i) n-BuLi, THF, −10 °C, (ii) 9-MeO-BBN; [III] 3.5 mol % $Pd(PPh_3)_4$, NaOH, THF, H_2O, rfx, 24 h.

Scheme 64

directed *ortho*-metallation chemistry of a nicotinamide leading to the lithiated species, which was quenched with 9-MeO-BBN. The Suzuki coupling was effected with 2-iodoaniline.[86]

D.i.b. *Alkenylation*

Tin Derivatives. Alkenylation by the Stille methodology using 4-pyrimidinylstannanes furnishes the 4-alkenylated pyrimidines **159** and **160** in good yields (**Scheme 65**).[83]

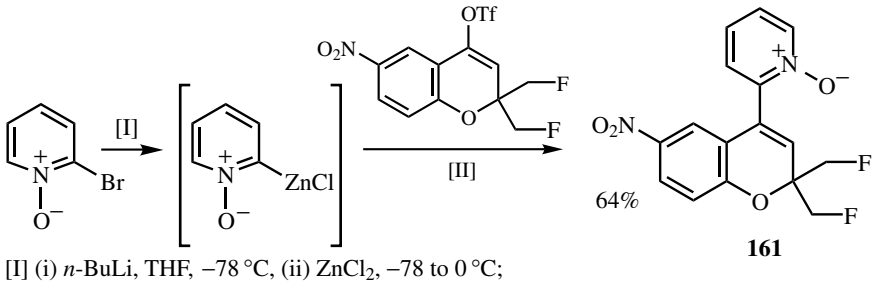


[I] 3 mol % $Cl_2Pd(PPh_3)_2$, DMF, rfx, 3 h; [II] 3 mol % $Cl_2Pd(MeCN)_2$, DCE, rfx, 4 h.

Scheme 65

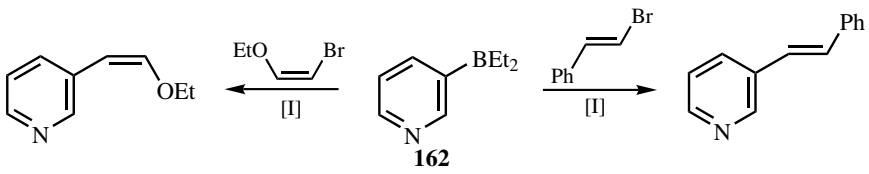
Zinc Derivatives. 2-(Benzopyran-4-yl)pyridine *N*-oxide has been prepared from 2-chlorozinciopyridine *N*-oxide and benzopyran-4-yl triflate in a Negishi-type coupling from 2-chlorozinciopyridine *N*-oxide (**Scheme 66**). A five-fold excess of the the zincated pyridine *N*-oxide had to be used for optimal formation of the cross-coupled product **161**.[90]

Boron Derivatives. Diethyl(3-pyridinyl)borane **162** can be alkenylated under Suzuki conditions (**Scheme 67**).[91]



[I] (i) *n*-BuLi, THF, −78 °C, (ii) $ZnCl_2$, −78 to 0 °C;
[II] 1.2 mol % $Pd(PPh_3)_4$, THF, r.t., 21 h.

Scheme 66

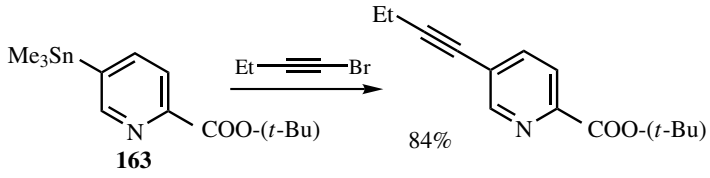


[I] mol % $Pd(PPh_3)_4$, THF, KOH, $(n\text{-}Bu)_4$ NBr, rfx, 1 h.

Scheme 67

D.i.c. *Alkynylation*

Tin Derivatives. 5-Alkynylpyridines can be prepared by a Stille-type reaction between a 1-bromoalkyne and a 5-trimethylstannylpyridine **163** (**Scheme 68**).[92]

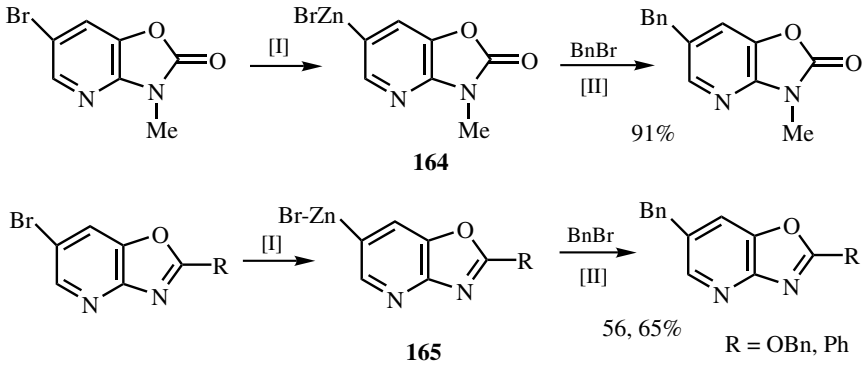


[I] 5 mol % $Pd(PPh_3)_4$, benzene, rfx, 48 h.

Scheme 68

D.i.d. *Alkylation*

Zinc Derivatives. Direct zincation of 6-bromoxazolo[4,5-*b*]pyridines can be effected using activated zinc (**Scheme 69**). The zincated species **164** and **165** from oxazolo[4,5-*b*]pyridin-2(3*H*)-ones or 2-phenyl- or 2-benzyloxyoxazolo[4,5-*b*]pyridines were used in Negishi-type coupling in a one-pot reaction with benzyl bromide for the preparation of 6-benzyl derivatives.[93]

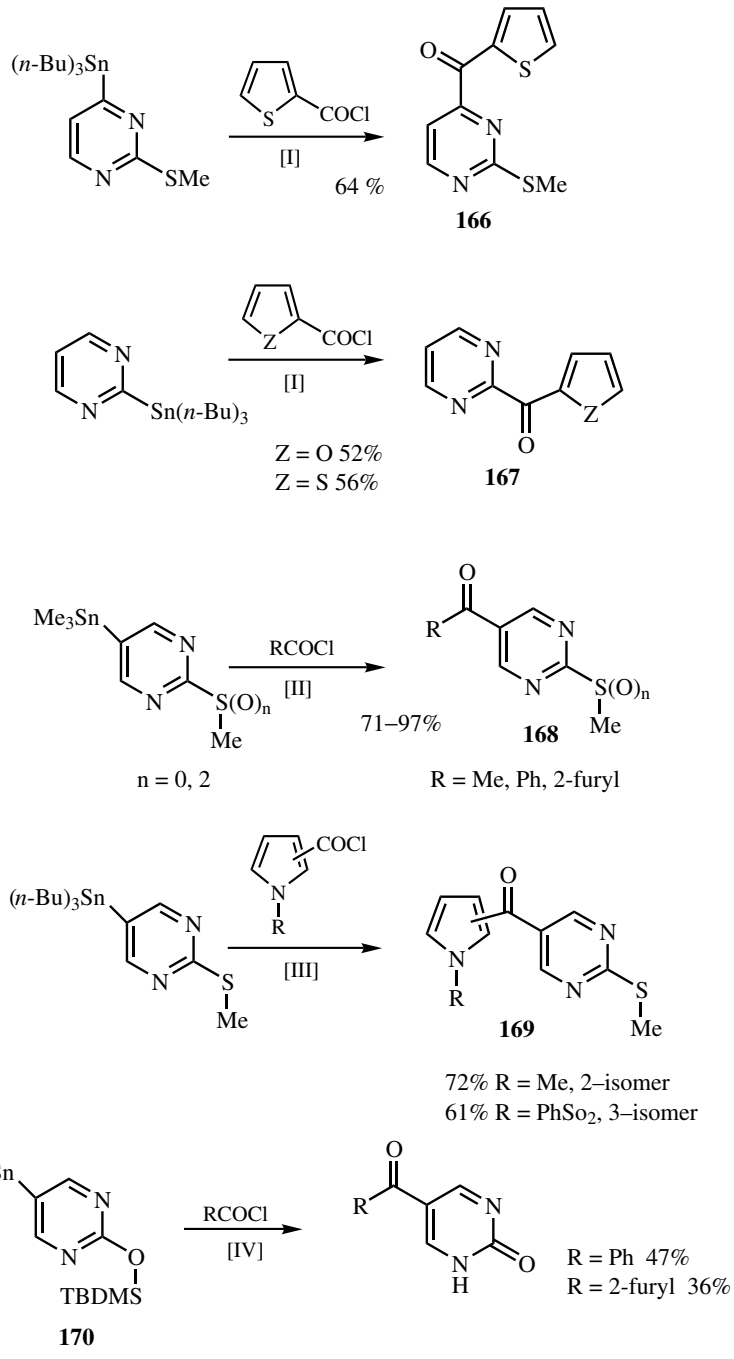


[I] Zn*, $(CH_2Br)_2$, TMSCl, THF; [II] 1 mol % $Pd(PPh_4)_2$, THF, 50 °C, 20 min.

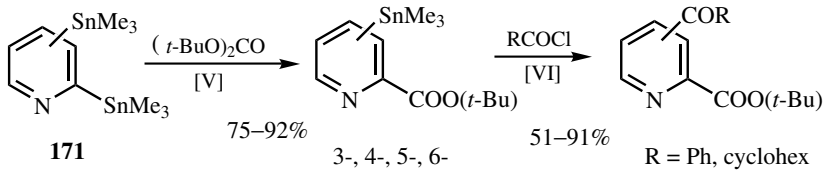
Scheme 69

D.i.e. *Carbonylation and Acylation*

Tin Derivatives. 4-Stannylpyrimidines are highly active in coupling reactions at low temperature and will couple with an acid chloride to form ketones **166** in the absence of a catalyst (**Scheme 70**). 2-Stannylpyrimidines also react rapidly with acid chlorides to form ketones **167** in the absence of a catalyst.[94] Alkyl, aryl, and heteroaryl ketones in the benzenoid 5-position **168** are available from 5-stannylpyrimidines and carbonyl chlorides. The trimethylstannyl derivatives gave consistently slightly higher yields than the tri(*n*-butyl)stannyl pyrimidines. The reaction with pyrroles was run on *N*-alkylated or *N*-acylated


(n-Bu)3Sn
SMe
COCl
[I]
64 %
166
Sn(n-Bu)3
Z = O 52%
Z = S 56%
167
Me3Sn
RCOCl
[II]
S(O)n
Me
71–97%
168
n = 0, 2
R = Me, Ph, 2-furyl
[III]
169
72% R = Me, 2–isomer
61% R = PhSo2, 3–isomer
TBDMS
170
[IV]
R = Ph 47%
R = 2-furyl 36%

Scheme 70



[I] THF, −78 °C, 0–5 min; [II] 7 mol % $Cl_2Pd(PPh_3)_2$, DCE or THF, rfx, 2–6 h; [III] 4 mol % $Cl_2Pd(PPh_3)_2$, THF, rfx, 6 h; [IV] 4 mol % $Cl_2Pd(PPh_3)_2$, DCE, rfx, 20 h; [V] benzene , rfx, 12–48 h; [VI] 5 mol % $Pd(OAc)_2$ or $Pd(PPh_3)_4$, benzene, rfx, 8 h.

Scheme 70 (*Continued*)

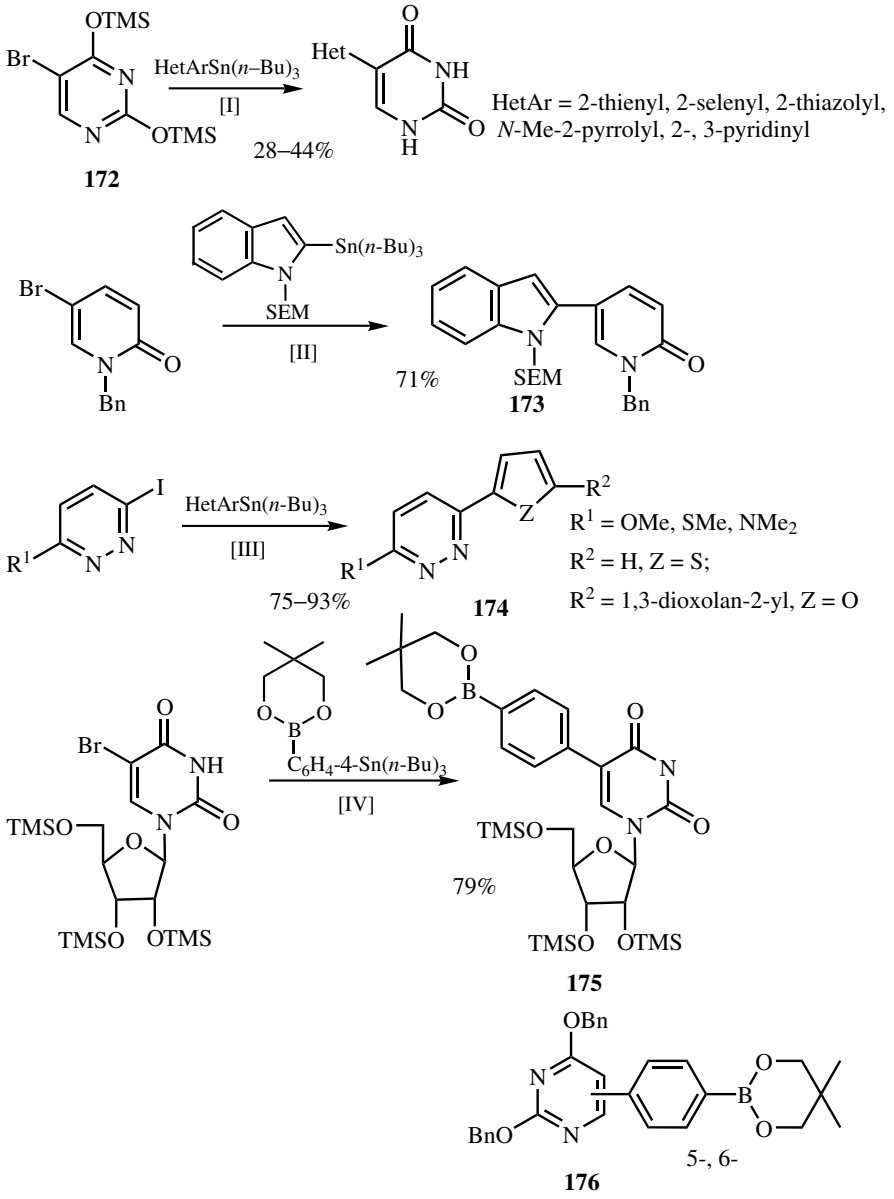
pyrrolocarbonyl chlorides to furnish the corresponding ketones **169**.[95] 2-Pyrimidinones are protected and solubilized as a *t*-butyldimethylsilyl ether **170** before coupling. During the reaction the silyl group is cleaved off. The products were isolated as pyrimidinones. The silyl function in the 5-acylated pyrimidine product is sensitive to cleavage because of the electron-withdrawing properties of the acyl group.[96]

A method for the introduction of different carbon functional groups, acyl and *tert*-butoxycarbonyl groups, in the pyridine ring has been described. The substrate is a bis(trimethylstannyl)pyridine **171**. The stannyl group in the electrophilic 2-position is replaced directly by an electrophile such as a *t*-butyloxycarbonyl group by heating the distannane with di-*t*-butyl dicarbonate. The remaining stannyl group is subjected to Stille-type coupling with an acid chloride to furnish the corresponding ketone. Alternatively, the 6-isomer, which has the stannyl group in the electrophilic 6-position, can be converted to the 6-ketone by heating with the acid chloride in the absence of a Pd catalyst.[92]

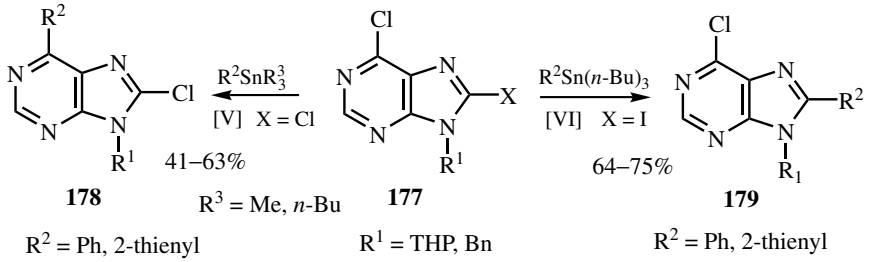
D.ii. Halogeno- or Triflyloxy-Substituted Six-Membered Ring Systems

D.ii.a. *Arylation*

Tin Reagents. Modest yields of coupling products were obtained from reactions of 2-thienyl- and 2-selenylstannanes with unprotected iodouracil. Silyl protected 5-bromouracil **172** reacts with formation of a number of biheteroaryl derivatives (**Scheme 71**).[97] In the preparation of 5-(2-indolyl)pyridin-2-ones **173** by Pd-catalyzed cross-coupling of 5-bromopyridin-2-ones, SEM-protected 2-indolylstannanes are better reagents than the corresponding 2-indolylzinc halides.[98] Coupling into pyridazines using 3-iodo derivatives and stannyl-thiopenes or -furan gives disubstituted pyridazines **174**.[99] Coupling between silyl-protected 5-bromouridine and arylstannanes containing a boronic acid substituent in the aryl group proceeds chemoselectively at the C—Sn bond rather than at the C—B bond to give boron-containing nucleosides **175**. The methodology was developed to provide boron-10 containing nucleosides for neutron-capture therapy. The same conditions can be used to introduce the benzeneboronic acid moiety into the 5-position of *O*-benzyl-protected 5-iodouracil **176**, and into the 6-position in *O*-benzyl-protected 6-bromouracil.[100] The 6-position in *N*9-substituted purines is more electrophilic than the 8-position. Hence, the 6,8-dichloropurines **177** can be selectively monoarylated in the 6-position under Stille conditions, the product being **178**. In the 6-chloro-8-iodo derivative the regioselectivity for monoarylation is reversed, and the 8-aryl derivatives **179** are obtained in a monosubstitution reaction.[101]


OTMS
Br
N
N
OTMS
HetArSn(n–Bu)3
[I]
28–44%
Het
O
NH
N
H
O
HetAr = 2-thienyl, 2-selenyl, 2-thiazolyl,
N-Me-2-pyrrolyl, 2-, 3-pyridinyl
172
Sn(n-Bu)3
N
SEM
Br
N
Bn
O
[II]
71%
N
SEM
173
N
Bn
O
I
R1
N
N
HetArSn(n-Bu)3
[III]
75–93%
R2
Z
R1
N
N
174
R1 = OMe, SMe, NMe2
R2 = H, Z = S;
R2 = 1,3-dioxolan-2-yl, Z = O
O
B
O
C6H4-4-Sn(n-Bu)3
[IV]
O
B
O
Br
NH
N
O
TMSO
O
TMSO
OTMS
79%
O
N
N
O
TMSO
O
TMSO
OTMS
175
OBn
N
BnO
N
O
B
O
5-, 6-
176

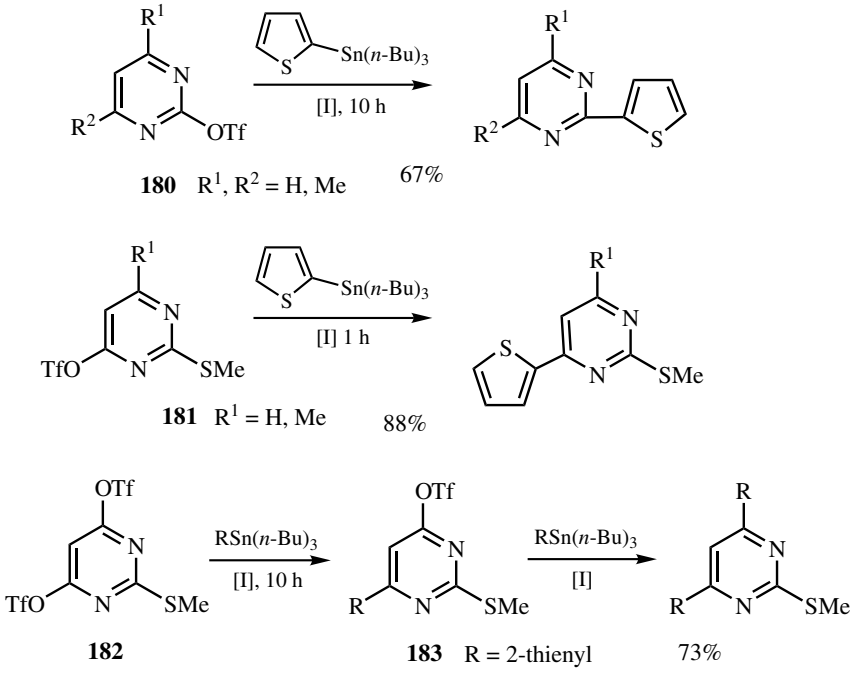
Scheme 71



[I] 5 mol % $Cl_2Pd(PPh_3)_2$, THF, rfx, 20 h; [II] 5 mol % $Pd(PPh_3)_4$, DMF, 110 °C; [III] 5 mol % $Cl_2Pd(PPh_3)_2$, DMF, 80 °C, 2 h; [IV] 5 mol % $Pd(PPh_3)_4$, toluene, rfx, 24 h; [V] 5 + 2.5 mol % $Pd(PPh_3)_4$, DCE, 60 °C to rfx, 24–30 h; [VI] 5 mol % $Pd[P(2\text{-furyl}])_3]_4$, DMF, 60–85 °C, 2.5–18 h.

Scheme 71 (*Continued*)

Pyrimidine has been triflated in the 2- and in the 4-position, and in both the 4/6-positions.[102] Pyrimidinyl triflates show reactivity comparable to chlorides in electrophilic positions with stepwise coupling. Thus, the ditriflate **182** (**Scheme 72**) can be monocoupled to the 4-thienyl derivative **183**, which reacts further to the dithienyl derivative. The higher reactivity in the 4-position as compared with the 2-position is also seen in the time required for completion of the coupling reactions by the two isomers. It is recommended that the triflation of pyrimidinones is carried out at low temperature (−78 °C). Thereafter

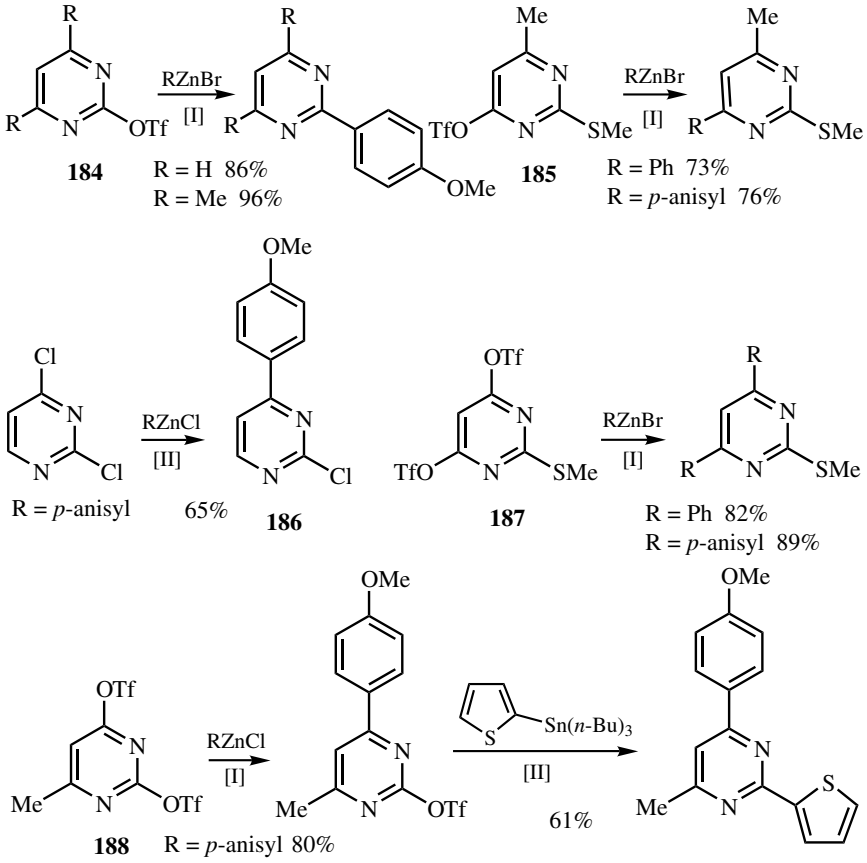


[I] 3 mol % $Pd(PPh_3)_4$, LiCl, dioxane, rfx.

Scheme 72

the temperature is raised slowly to room temperature. Triflation carried out in this manner gives products stable for purification by preparative chromatography.[102]

Zinc Reagents. The pyrimidinyl triflates show comparable reactivity to the chloropyrimidines in Pd-catalyzed reactions with organozinc reagents. High yields result from coupling reactions with 2-triflyloxypyrimidines **184** and 4-triflyloxypyrimidines **185** (**Scheme 73**). 2-Methylthiopyrimidinyl 4,6-ditriflate **187** reacts with arylzinc reagents to give dicoupled products.[102] In the reaction between 4-anisylzinc bromide and 2,4-dichloropyrimidine, it is the 4-position that is the more reactive, and the monoarylated 4-anisyl derivative **186** is formed using 1 equiv of the zinc reagent.[103] The regioselectivity is the same as observed for the corresponding triflates and for Pd-catalyzed reactions of the dichloride with stannanes.[104] The chlorine in the 2-position can also be replaced by an excess of reagent. Another zinc or tin reagent would give a pyrimidine product with two different carbosubstituents. In the 2,4-ditriflate **188**, the initial reaction is at the more electrophilic 4-position, as for the corresponding 2,4-dichloride. With excess *p*-anisylzinc bromide the disubstituted product is formed. The intermediate monoarylated product has



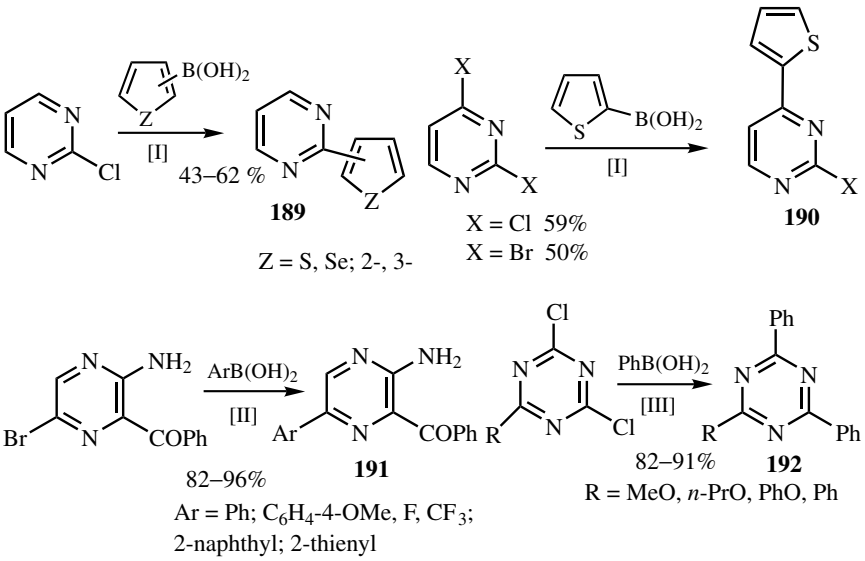
[I] 3 mol % $Pd(PPh_3)_4$, LiCl, dioxane, rfx, 2 h; [II] 2 mol % $Pd(PPh_3)_4$, THF, rfx, 1–2 h.

Scheme 73

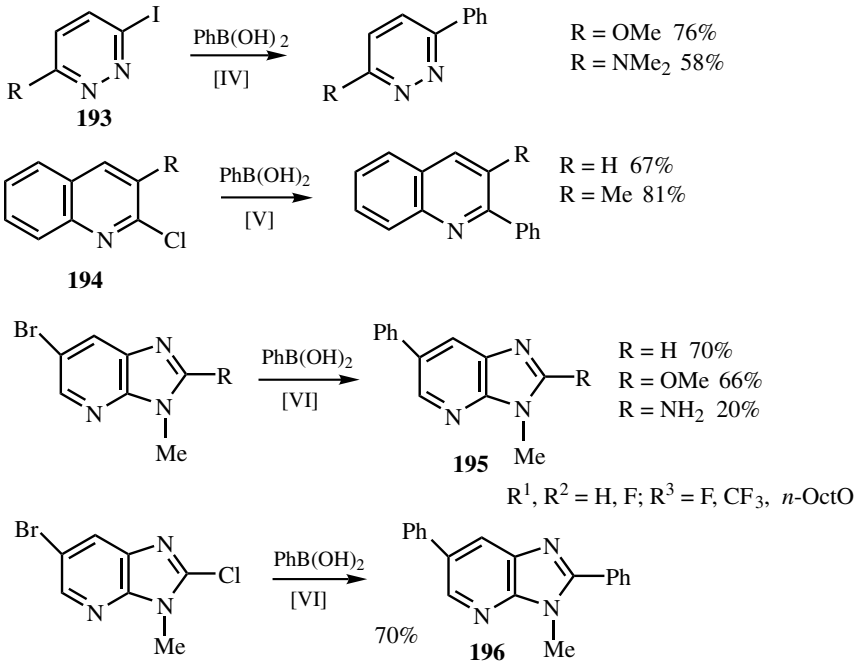
been reacted further under Stille conditions with 2-tri(*n*-butyl)stannylthiophene under Pd catalysis and gives the 2-thienyl derivative.[103]

Boron Reagents. Cross-coupling reactions between organoboranes and simple pyrimidines are illustrated by the reaction between 2-chloropyrimidine and 2- or 3-thiophene- and selenophene-boronic acids, which gives the corresponding 2-substituted pyrimidines **189** (**Scheme 74**). In 2,4-dichloro- or 2,4-dibromopyrimidine it is the 4-halogeno substituent that is the more reactive, 2-chloro- or 2-bromo-4-(2-thienyl)pyrimidine **190** being the product from the coupling with thiophene-2-boronic acid.[105] It was necessary to protect 5-bromo- or 5-iodouracil before coupling; *t*-butyl and benzyl derivatives of the uracils were used in the preparation of the biheteroaryls.[97] 2-Amino-3-benzoyl-5-bromopyrazine gives excellent yields of cross-coupled product **191** with arylboronic acids.[106] Symmetrically and unsymmetrically 2-substituted 4,6-diphenyl-1,3,5-triazines **192** have been prepared by the Suzuki reaction from 2-substituted 4,6-dichloro-1,3,5-position using benzeneboronic acid.[107] 3-Iodopyridazines **193** are coupled in the same manner.[99] Arylation in 2-chloroquinolines **194** proceeds well because the chlorine substituent is located in an electrophilic quinoline position.[108] Benzeneboronic acid has been coupled with 2-chloro- and 6-bromo derivatives of 1- and 3-methylimidazo[4,5-*b*]pyridines to furnish the corresponding 2-phenyl and 6-phenyl derivatives **195**. The halogen in the 6-position should be a bromine or iodine for an easy coupling. The 6-bromo-2-chloro substrate gave 2,6-diphenylimidazo[4,5-*b*]pyridines **196** when an excess of benzeneboronic acid was used. If not, mixtures of monophenylated and diphenylated products were obtained. The imidazo[4,5-*b*]pyridine substrate had to be *N*-protected for the coupling reactions to proceed.[109]

Couplings in 5-bromo-2-chloropyrimidine would be expected to proceed preferentially in the 5-bromo position (**Scheme 75**). This order of preference has been changed by an initial exchange of the chloro with an iodo substituent. The product from the halogen exchange, 5-bromo-2-iodopyrimidine, is selectively coupled in the 2-position with a wide



Scheme 74 (*Continued*)



[I] 3 mol% $Pd(PPh_3)_4$, 1 M Na_2CO_3, glyme, rfx, 14; [II] (i) 5 mol % $Cl_2Pd(PhCN)_2$, dppb, toluene, r.t, 30 min, (ii) EtOH, H_2O, Na_2CO_3, toluene, rfx, 7 h; [III] 5 mol % $Pd(PPh_3)_4$, Na_2CO_3, H_2O, toluene, rfx, 48 h; [IV] 3 mol % $Pd(PPh_3)_4$, Na_2CO_3, H_2O, toluene, rfx, 12 h; [V] 2 mol % $Pd(PPh_3)_4$, BHT, $Ba(OH)_2$, THF, 75 °C, 1.5–2 h; [VI] 3 mol % $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, rfx, 2–5 h.

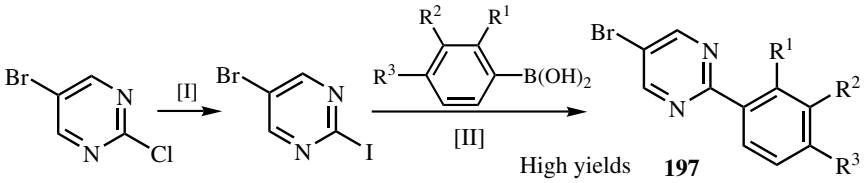
Scheme 74 (*Continued*)

range of arylboronic acids to provide substituted 2-pyrimidines **197**.[110] A catalyst system generated from palladium diacetate and 2-(di-*tert*-butylphosphino)biphenyl efficiently promotes Suzuki coupling at or close to room temperature of both π-electron-rich or electron-poor aryl bromides and chlorides with potassium fluoride as the base. Even a chlorine in the benzenoid 3-position in pyridine is replaced with high yield of the cross-coupled product **198**.[33]

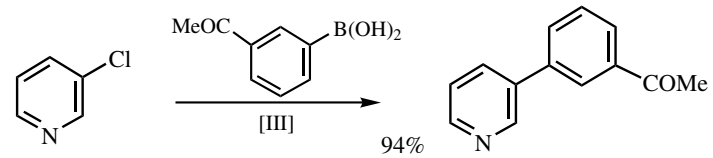
Selective *N*-quaternization or *N*-oxidation in a dipyridine system can be achieved indirectly by a cross-coupling between the two differently functionalized pyridine components as illustrated by the coupling reaction leading to the products **199**.[111]

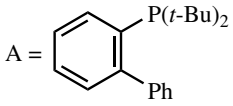
4-Arylated β-carbolines **200** are generated from the corresponding triflate under Suzuki conditions.[112]

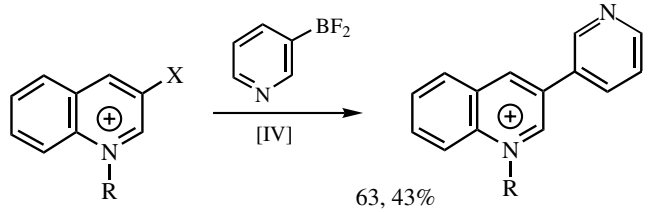
Homocoupling. In cross-coupling reactions a major by-product may arise from homocoupling. Homocoupling is effected in the absence of a second reaction partner. In the reactions of 3-bromoquinoline or 2-chloroquinoline under conditions for homocoupling, the products **201** are formed (**Scheme 76**).[113]



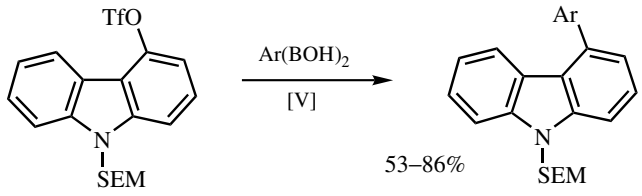
R^1, R^2 = H, F; R^3 = F, CF_3, *n*-OctO







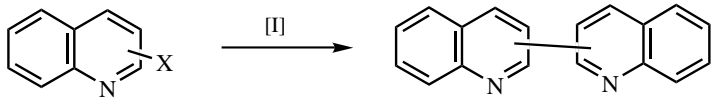
R = O^- (X = Br); Me (X = I)



Ar = Ph, C_6H_4-3-Me, C_6H_4-3-Cl, 2-naphthyl
= C_6H_4-4-OMe, $P(PPh_3)_4$ was used.

[I] 57% HI, CH_2Cl_2, 0 °C, 5 h; [II] $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O; [III] 1 mol % Pd(OAc), 2 mol % A, KF, THF, 50 °C, 9 h; [IV] 5 mol % $Pd(Ph_3)_4$, THF, H_2O, $NaHCO_3$, rfx, 8–36 h; [V] 5 mol % $Cl_2Pd(dppf)$, THF/dioxane, K_3PO_4, heat.

Scheme 75



X = 2-Cl, 3-Br

2,2′- 62%
3,3 ′79%

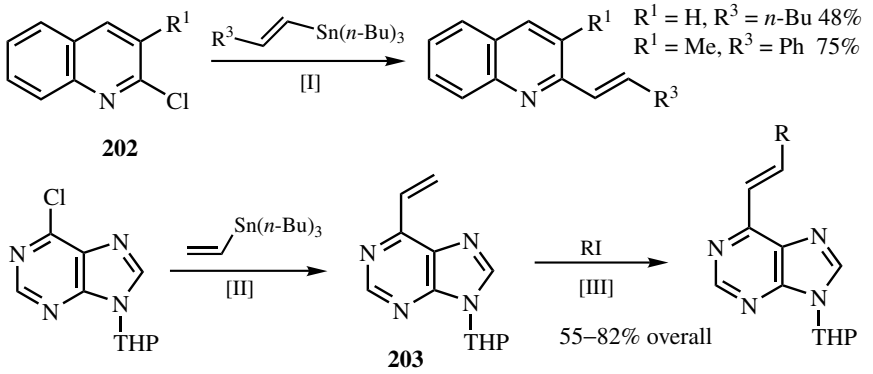
201

[I] 5 mol % $Pd(OAc)_2$, *i*-PrOH, $(n\text{-Bu})_4NBr$, K_2CO_3, DMF, 135 °C, 22 h (3-isomer), 96 h (2-isomer).

Scheme 76

D.ii.b. *Alkenylation*

Tin Reagents. The presence of a 3-methyl group in the 2-chloroquinoline **202** has a beneficial effect on reaction rates and efficiency in Stille-type alkenylations with terminal stannyl alkenes (**Scheme 77**). This was attributed to steric acceleration in the reductive elimination of Pd(0) from a Pd(II) complex.[108] The purine 6-position is highly electrophilic. A chloro substituent is readily replaced under Stille conditions using tri(*n*-butyl)vinylstannane. The 6-vinylpurine product **203** from the coupling is reacted further *in situ* in Heck couplings. These reactions proceed readily because of the electron-withdrawing effect from the π-deficient pyrimidine moiety of the heterocycle.[114]



202

203

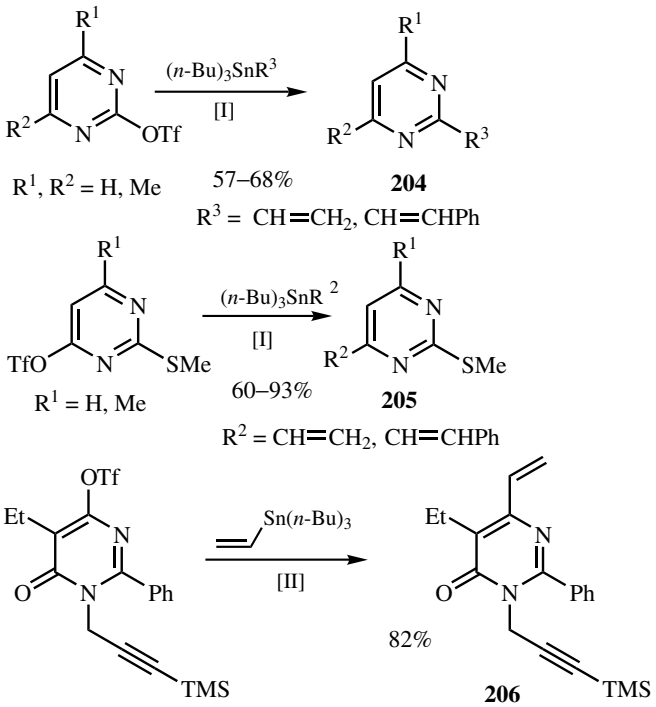
R = Ph; C_6H_4-4-Cl and OMe, 2-OH; 3-iodo- and 5-iodo-2-thienyl; 5-iodo-2-furyl; *trans*-$CHC(Me)CO_2Me$, *trans*-$CHC(Me)CH_2OH$

[I] 4 mol % $Pd(OAc)_2$, dppp, BHT, NEt_3, DMF, 80 °C, 24–36 h; [II] 5 mol % $Cl_2Pd(PPh_3)_2$, DCE, rfx, 5.5 h; [III] 5 mol % $Pd(OAc)_2$, $EtN(i\text{-}Pr)_2$, DMF, 55–85 °C, 3.5–24 h.

Scheme 77

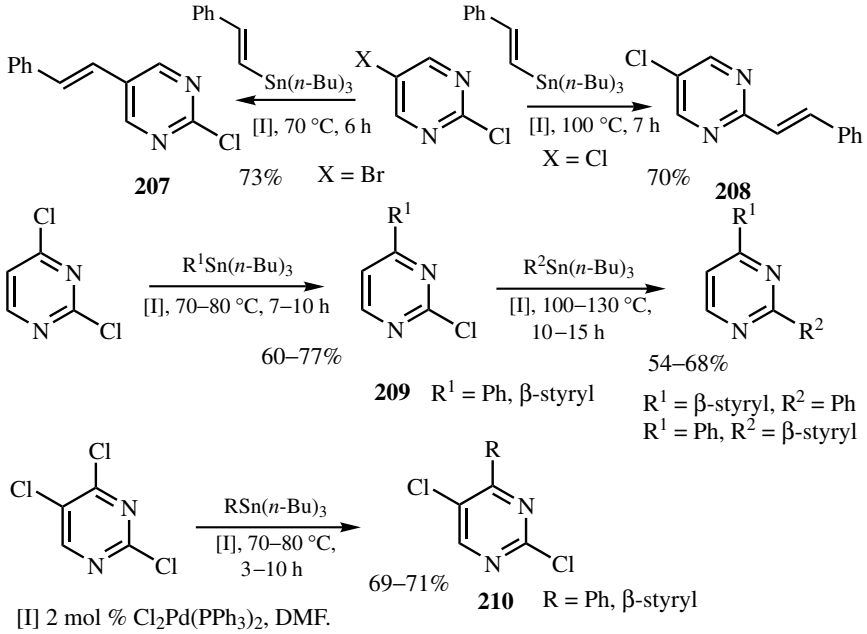
Both 2- and 4-pyrimidinyl triflates yield the respective coupling products **204** and **205** with vinylstannanes under Stille conditions (**Scheme 78**).[102] Another example is provided by Stille coupling between 6-triflyloxy-4(3*H*)-pyrimidinones and tri(*n*-butyl)vinyltin with formation of the 6-substituted-4(3*H*)-pyrimidinone **206**.[115]

5-Bromopyrimidines give 5-alkenyl derivatives when coupled with alkenylstannanes.[116] A chlorine in an electrophilic azine position, but not in a benzenoid position, can be replaced by a carbosubstituent (**Scheme 79**). The reaction between 2,5-dichloropyrimidine and styryltributylstannane occurs at the activated 2-position with formation of **208**.



[I] 3 mol % $Pd(PPh_3)_4$, LiCl, dioxane, rfx, 1–2 h (vinyl 14 h);
[II] $Pd(PPh_3)_4$, LiCl, dioxane, rfx.

Scheme 78

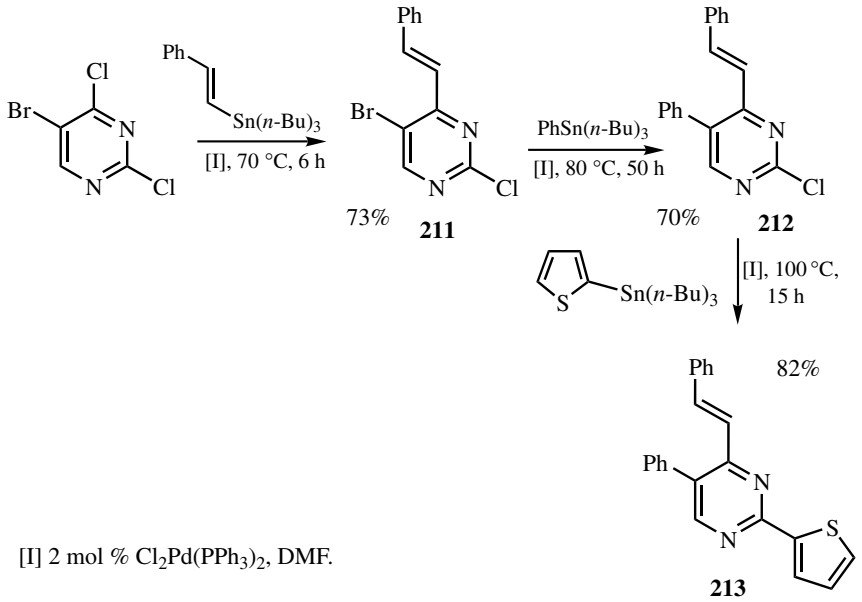


[I] 2 mol % $Cl_2Pd(PPh_3)_2$, DMF.

Scheme 79

5-Bromo-2-chloropyrimidine, however, is coupled selectively at the 5-position to form the product **207**. Phenylation by phenylstannanes takes place in the same regioselective manner (*vide supra*). In reactions of 2,4-dichloropyrimidine with β-styryl- or phenyl(tri-*n*-butyl)stannane, the carbosubstituent goes selectively into the 4-position **209**.[117] A second carbosubstituent can subsequently be introduced into the 2-position. The regioselectivity corresponds to the relative reactivity of pyrimidine toward heteronucleophiles. In 2,4,6-trichloropyrimidine one chlorine in the 4/6-position is replaced selectively **210** under conditions for monocoupling.

A good demonstration of the regio- and chemoselectivity in these reactions is provided by the stepwise introduction of three different carbosubstituents into 5-bromo-2,4-dichloropyrimidine (**Scheme 80**). Initial styrylation is in the 4-position **211**, subsequent phenylation is in the 5-position **212**, and finally thienylation is in the 2-position **213**.[117]



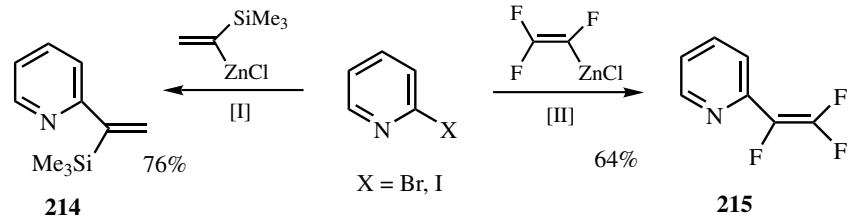
[I] 2 mol % $Cl_2Pd(PPh_3)_2$, DMF.

Scheme 80

Zinc Reagents. Negishi coupling of α-zincated vinyltrimethylsilanes with 2-bromopyridine yields 2-vinylpyridine functionalized by a silyl substituent at the α-carbon of the vinyl group **214** (**Scheme 81**).[118] Similarly, the trifluoroethenyl group has been substituted into the 2-position in pyridine **215** using zincated trifluoroethene and 2-iodopyridine.[119]

Aluminum Reagents. Alkenylaluminum compounds can also be used as reagents for alkenylation in reactions promoted by palladium. Formation of a 2-alkenylpyridine **216** is shown (**Scheme 82**).[120]

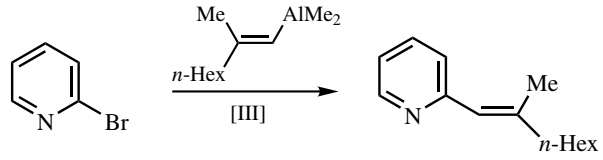
Zirconium Reagents. Ethenylation can be effected via hydrozirconated terminal alkynes (**Scheme 83**). The alkenylzirconocene gives the *E*-alkenyl product. The reaction is carried out in the presence of zinc chloride. Presumably metal metathesis occurs before the palladium-mediated coupling takes place. The coupling is regiospecific with initial



214 **215**

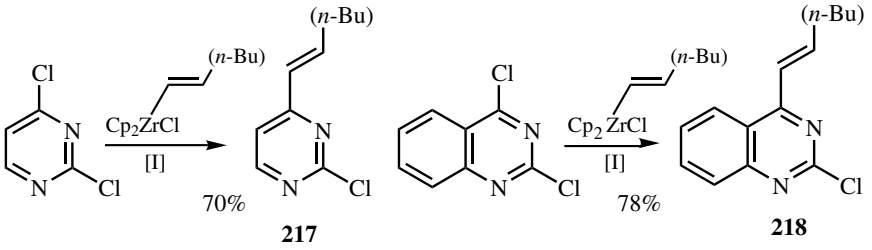
[I] 0.5 mol % $Cl_2Pd(dppb)$, THF, rfx, 2 h; [II] 3 mol % $Pd(PPh_3)_4$,THF-Et_2O, r. t.

Scheme 81



[I] 5 mol % $Pd(PPh_3)_4$, THF, 25 °C, 5 h. **216**

Scheme 82



217 **218**

[I] (i) 1-Hexyne, $Cp_2Zr(Cl)H$, benzene, r.t., 2 h, (ii) 5 mol % $Pd(PPh_3)_4$, 5 mol % $ZnCl_2$; THF, rfx, 20 h.

Scheme 83

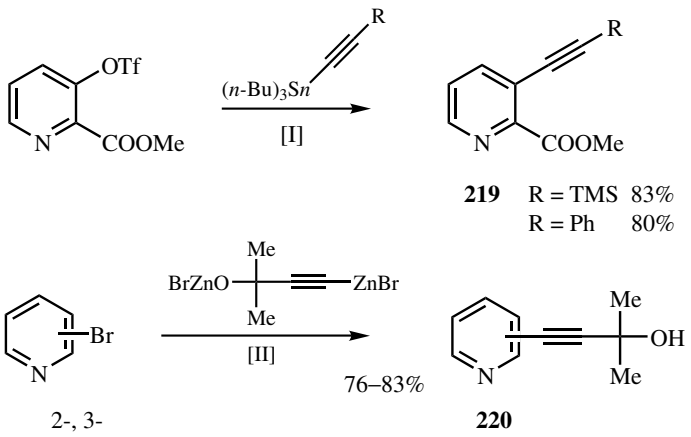
carbosubstitution in the more electrophilic 4-position in 2,4-dichloropyrimidine and 2,4-dichloroquinazoline with formation of the alkenylated products **217** and **218**, respectively.[121]

D.ii.c. *Alkynylation*

Tin and Zinc Reagents. Coupling under Sonogashira conditions is commonly used for ethynylation. Other methodologies are less popular but useful (**Scheme 84**). Under Stille conditions, a 3-pyridinyl triflate was coupled with 1-stannylalkynes to form the ethynyl derivatives **219**.[122]

Under Negishi conditions, a monoprotected ethynylzinc reagent was used for the preparation of ethynylpyridines **220** by coupling with the respective bromopyridines.[40]

Copper Reactants. Sonogashira coupling of vicinal halogenopyridine-carbonitriles can be used for preparation of the corresponding alkynylated pyridines (**Scheme 85**). The products



[I] 5 mol % $Pd(PPh_3)_4$, LiCl, dioxane, 80 °C, 2–14 h; [II] 5 mol % $Pd(PPh_3)_4$, THF, DMF, 50 °C, 5–24 h.

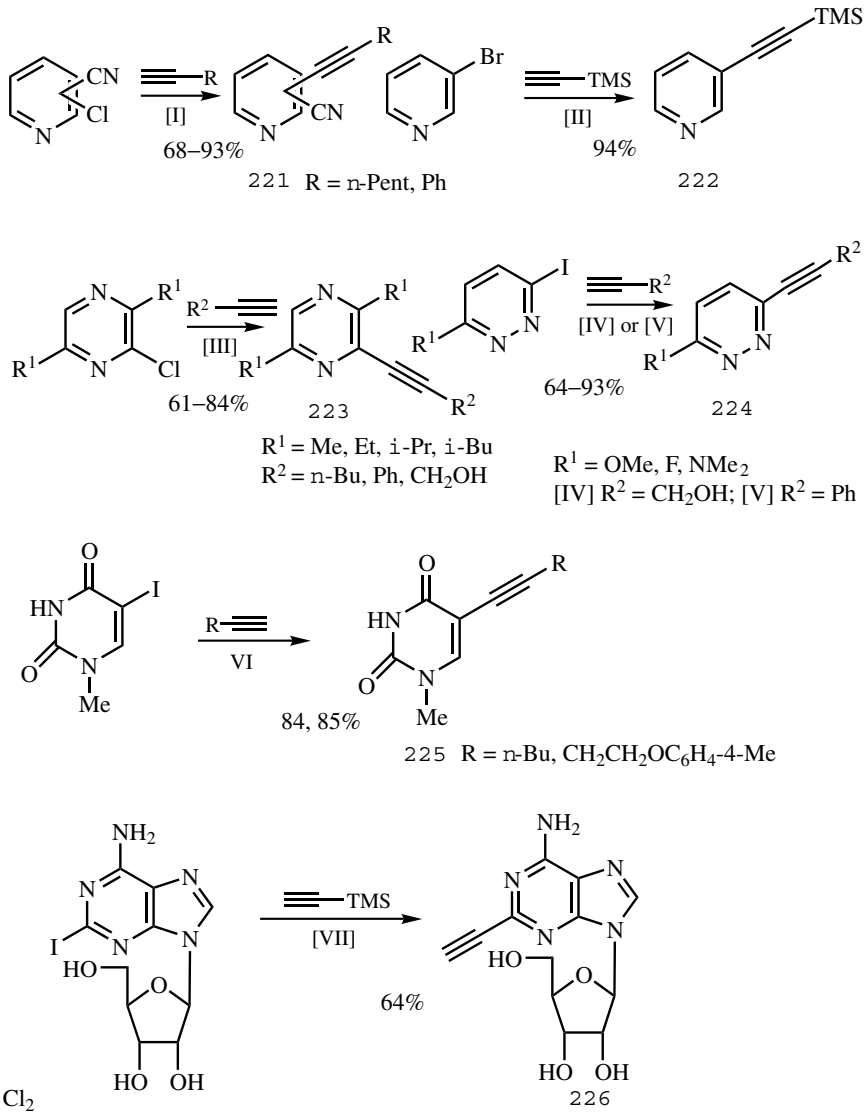
Scheme 84

221 are generally formed in high yields.[123] 3-Bromopyridine is ethynylated in the benzenoid 3-position **222**.[37] 3,6-Dialkyl-2-chloropyrazines form the cross-coupled products **223**. Their *N*-oxides were coupled under similar conditions.[124] 3-Iodopyridazines were used as substrate for the preparation of 3-ethynylated pyridazines **224**.[99] Treatment of 5-iodo-1-methyluracil with terminal alkynes under Sonogashira conditions results in the formation of 5-alkynyl derivatives **225**. This reaction easily proceeds further with cyclization to 6-substituted 3-methylfurano[2,3-*d*]pyrimidin-2-ones (*vide infra*).[125] The ethynylation methodology has also been used for the preparation of C-2 alkynylated adenosine **226** from the 2-iodo derivative. The reaction with monosilylated acetylene was run without protection of the functional groups in the nucleoside.[126]

In the 4-chloro-5-iodopyrimidine **227** the iodine in the 5-position is selectively displaced in the alkynylation, and in the 5-chloro-4-iodo isomer coupling is in the 4-position (**Scheme 86**).[127] In silyl-protected 5-chloro-4-iodopyrimidin-2-one **228** hydrolysis of the silyl ether function during the alkynylation reaction was prevented by the use of hexamethyldisilazane as a trapping agent for adventitious water.[128] In the quinazoline series, at room temperature, selective alkynylation can be effected in the more reactive 4-position in 2,4-dichloroquinazoline to provide the product **229**. The second alkynyl group is substituted into the 2-position on slight warming of the reaction mixture. The same regioselectivity for alkynylation is achieved in 2,4-dichloropyrimidine. In 6-bromo-2,4-dichloroquinazoline competitive reactions between the 4-chloro position and the 6-bromo position led to a mixture of the corresponding hexynynyl derivatives **230**. Either product is a substrate for the introduction of two additional alkynyl groups to furnish the trialkynylated quinazoline **231**.[121]

Vicinal diynes have been prepared as intermediates for subsequent cyclization studies (**Scheme 87**). Monoprotected acetylene was used. Coupling with 2,3-dichloroquinoxaline gave the dialkyne **232**. The vicinal pair in the pyridine **233** was a bromo and a triflyloxy substituent, and in the pyrimidine **234** a chloro and an iodo substituent. The dialkynylated products were obtained in modest to good yields.[129]

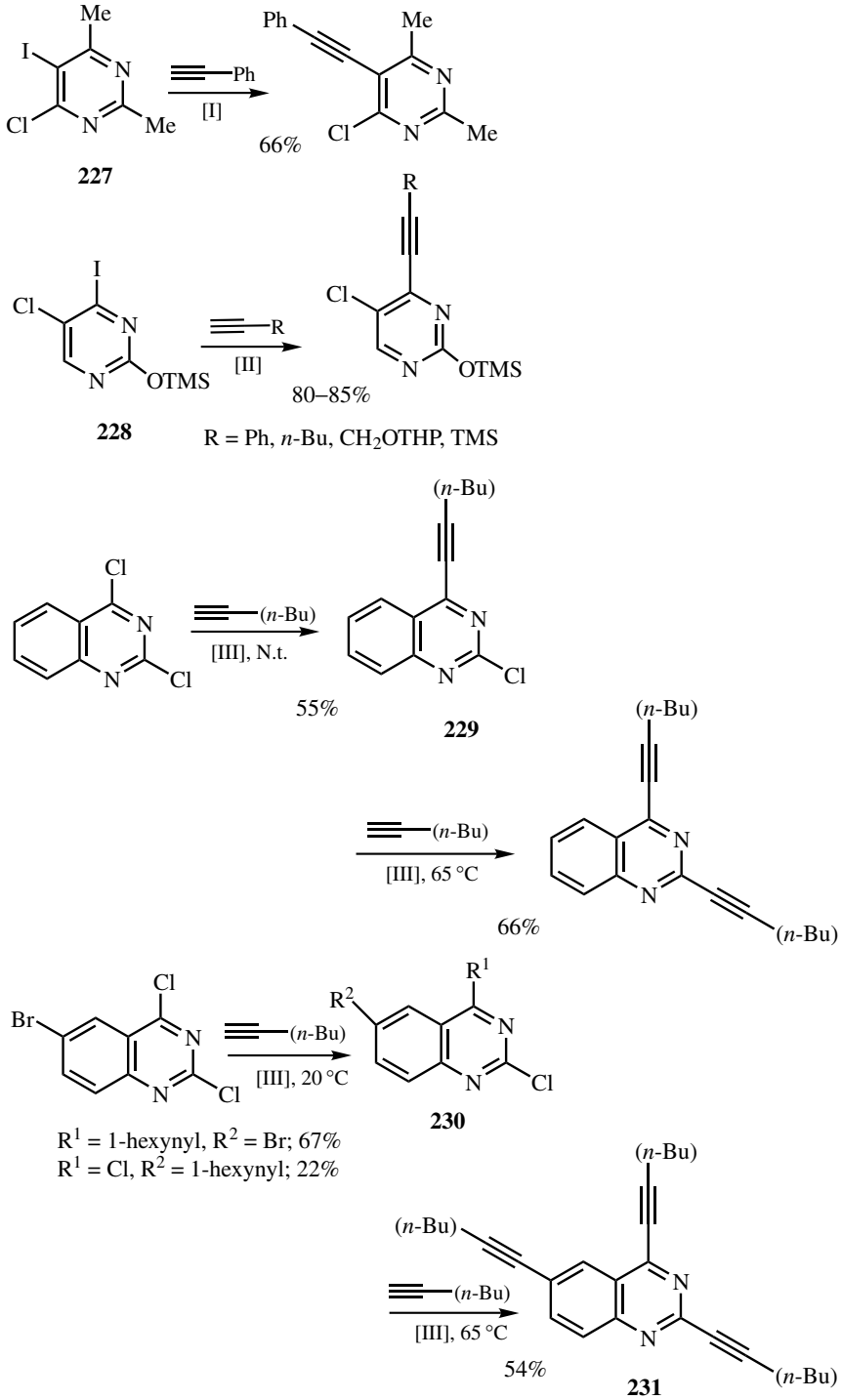
With free acetylene, coupling at both termini is readily achieved as illustrated by the preparation of ethynyl-bridged bipyridine **235** (**Scheme 88**).[37]. This is an example of a



[I] 2.5 mol % $Cl_2Pd_2(PPh_3)_2$, CuI, NEt_3, 10 °C, 4–6 h; [II] 4 mol % $Cl_2Pd_2(PPh_3)_2$, CuBr, NEt_3, rfx, 1 h; [III] 5 mol % $Pd(PPh_3)_4$, DMF, AcOK, 100 °C, 2 h; [IV] 3 mol % $Pd(PPh_3)_2$, CuI, NEt_3, THF, r.t., 8 h; [V] 5 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, DMF, r.t., 8 h; [VI] 1 mol % $Cl_2Pd_2(PPh_3)_2$, CuI, NEt_3, 50 °C, 1.5, 2 h; [VII] 8 mol % $Pd(PPh_3)_4$, CuI, TEA, DMF, 80 °C, 70 min.

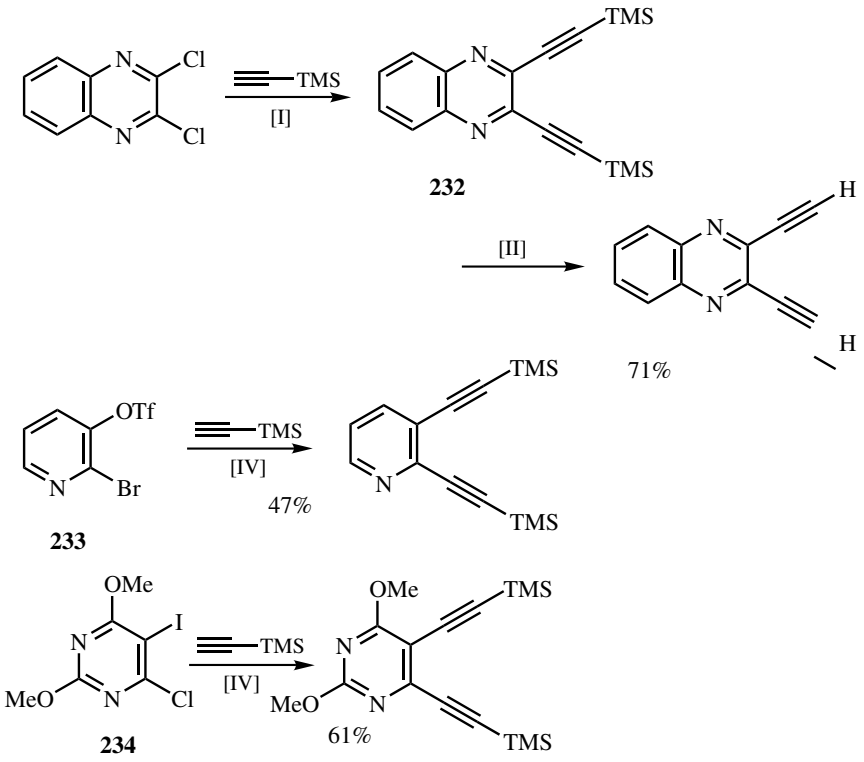
Scheme 85

general reaction for disubstitution. With metallated free acetylene a mixture from monoarylation and diarylation is normally the case unless conditions have been chosen for diarylation. A recent study shows that the metal in the metaloacetylene as well as the nature of the heterocyclic substituent are important for the control of the two reaction modes, which lead to the products **236** and **237**.[40]



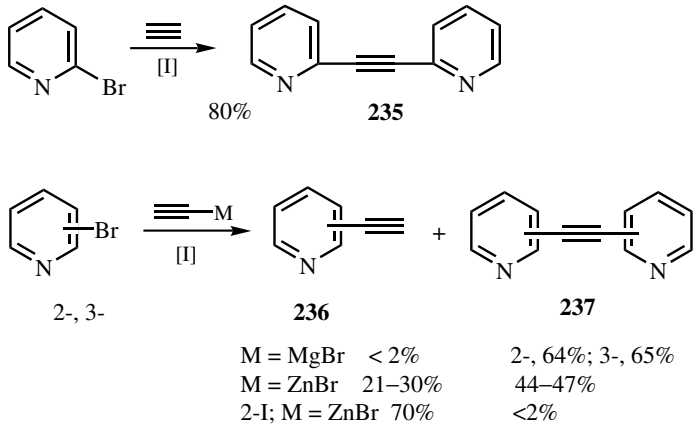
[I] 2 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, N.t.; [II] 1 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, HMDS, 20 °C; [III] 2 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, 20 h.

Scheme 86



[I] 10 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, 100 °C, 10 h; [II] HF-NaF buffer pH 5.5, H_2O, r.t., 14 h; [III] 10 mol % $Pd(PPh_3)_4$, CuI $(i\text{-Pr})_2NH$, 100 °C, 13 h; [IV] as

Scheme 87

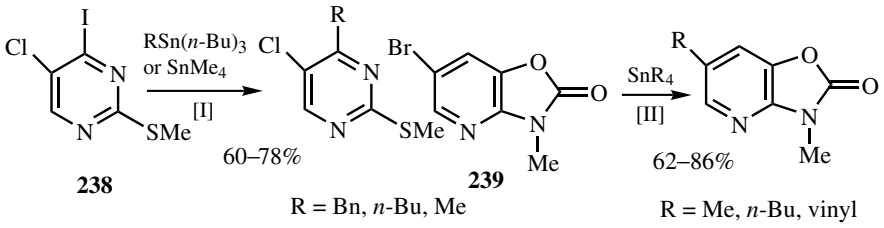


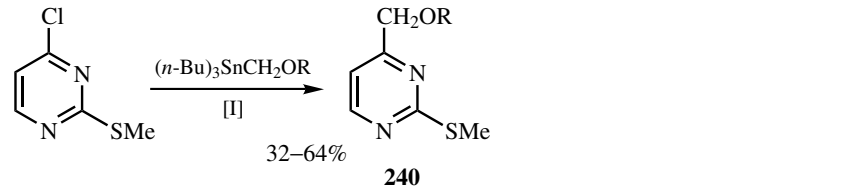
[I] 3 mol % $Pd(PPh_3)_4$, PPh_3, CuI, $NHEt_2$, rfx, 2 h; [II] 5 mol % $Pd(PPh_3)_4$, THF, DMF, 50 °C, 5–24 h.

Scheme 88

D.ii.d. *Alkylation*

Tin Reagents. In stannanes sp^3-hybridized carbon attached directly to the metal is less reactive than sp^2- or sp-hybridized carbon in the transfer process to the Pd(II) intermediate in the catalytic cycle. Tetramethyl- or tetrabutylstannane can be used for the preparation of methyl and butyl derivatives (**Scheme 89**), but these reactions often require vigorous conditions. A successful reaction is shown for a 4-iodopyrimidine **238**.[130] In another case a bromine substituent in a benzenoid β-position in an oxazoloannulated pyridine **239** has been substituted by this methodology.[131] The reactivity is enhanced when the sp^3-hybridized carbon carries an electronegative group or unsaturation. Therefore, in the reaction between benzyltri(*n*-butyl)stannane and the iodopyrimidine **238** it is the benzyl group that is transferred to the pyrimidine. An electronegative substituent in the alkyl group to be transferred is seen in the reaction between the methyl- or silyloxymethyltri(*n*-butyl)stannane and a 4-chloropyrimidine to form the 4-pyrimidinemethyl ethers **240**.[83] Alkylzinc or alkylaluminum reagents may be a better choice for simple alkylation reactions.

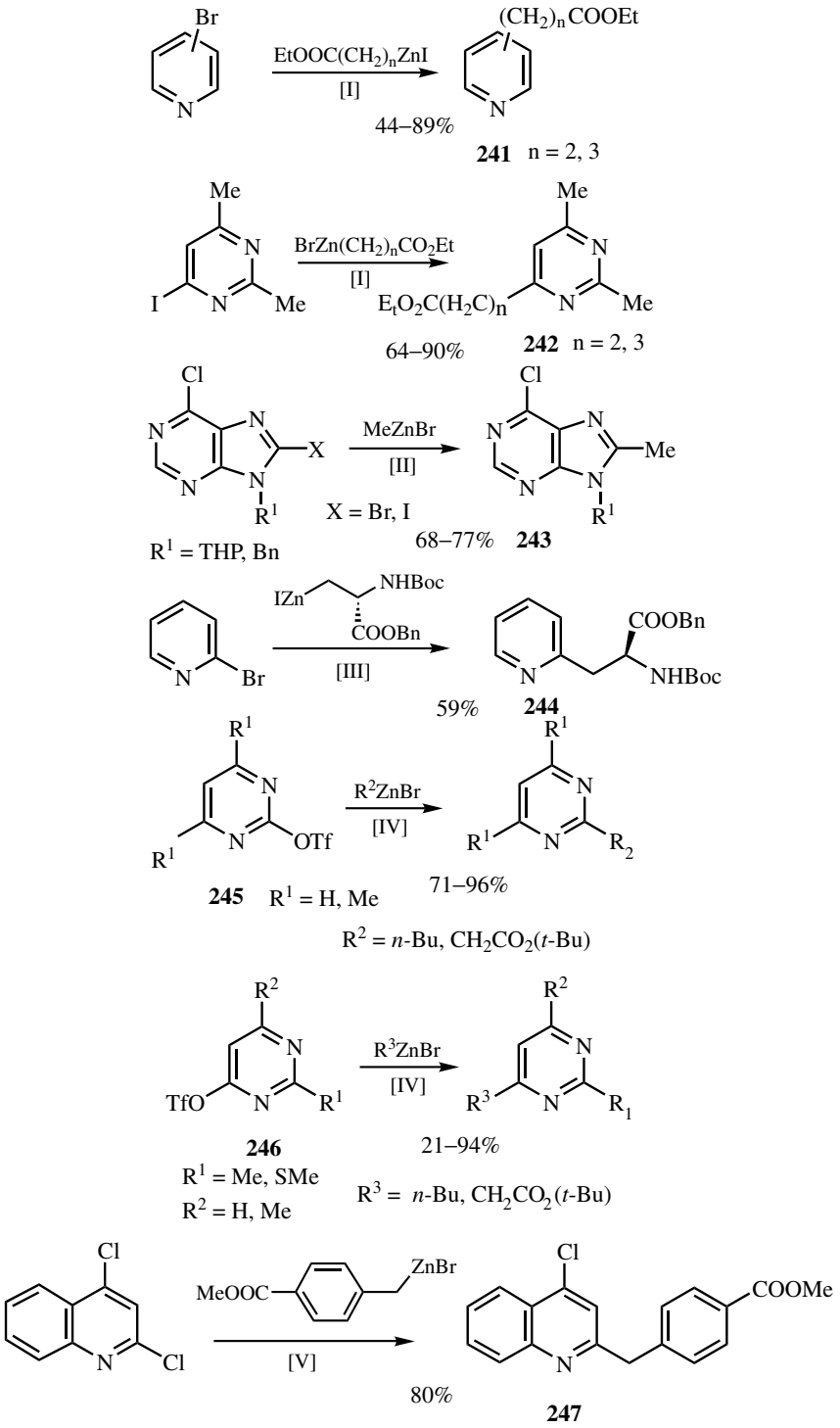




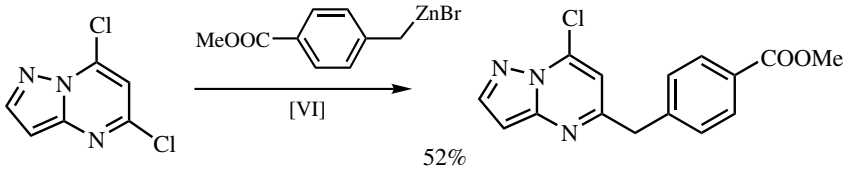
[I] 2 mol % $Cl_2Pd(PPh_3)_2$ DMF, 100–120 °C, 15 h (for Me_4Sn: 70 °C, 2 d); [II] 1–3 mol % $Cl_2Pd(PPh_3)_2$, toluene, 110 °C, 8 h; [III] 2 mol % $Cl_2Pd(PPh_3)_2$, DMF, 90 °C, 12–24 h.

Scheme 89

Zinc Reagents. Bromo- and iodopyridines and bromo- and iodopyrimidines can be alkylated using organozinc reagents. Ethoxycarbonylalkylzinc iodides, prepared from the corresponding alkyl iodides with zinc–copper couple, react under mild conditions to form the alkylated products **241** and **242** (**Scheme 90**).[132] 6-Chloro-8-bromo- or 8-iodopurines are selectively methylated in the 8-position **243** using methylzinc bromide.[101] By similar methodology, the organozinc iodide derived from appropriately protected serine as original substrate can be coupled into the 2-position in pyridine to furnish a pyridine analog **244** of the amino acid phenylalanine in moderate yield.[133] A wide range of amino acids can in principle be prepared by this methodology. The choice of catalyst is important for many of these reactions, and $Cl_2PdP(o\text{-tol})_3)_2$ has been found



Scheme 90 (*Continued*)



52%

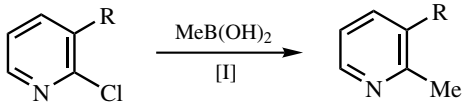
248

[I] 4 mol % $Cl_2Pd(PPh_3)_2$, benzene/DMF, r.t., 0.5−1 h; [II] 2.5 mol % $Pd[P(2\text{-furyl}])_3]_4$, THF, 60 °C, 4 h; [III] 5 mol % $Cl_2Pd[P(o\text{-tol})_3]_2$, DMAC/benzene, sonification 22 −35 °C, 30 min; [IV] 3 mol % $Pd(PPh_3)_4$, THF, rfx, 2 h; [V] 5 mol % $Pd(PPh_3)_4$, THF, 60 °C, 2 h; [VI] 4 mol % $Pd(PPh_3)_4$, DMF, 60 °C, 4 h.

Scheme 90 (*Continued*)

to be highly effective.[133] Triflates are equally useful in the cross-coupling with organozinc reagents as shown by alkylation of 2-pyrimidinyl triflates **245** and the 4-pyrimidinyl triflates **246**.[102] 2,4-Dichloroquinoline is coupled regioselectively with benzylic zinc reagents under palladium-mediated conditions in the α-position to yield the product **247**. With added lithium chloride in the absence of the palladium catalyst, substitution is in the 4-position. 5,7-Dichloropyrazolo[1,5-*a*]pyrimidine reacts similarly with α-substitution under palladium-mediated conditions to furnish the product **248** and replacement of the 4-chloro substituent in the absence of the palladium catalyst.[134]

Boron Reagents. The Suzuki coupling with methylboronic acid and 2-chloro-3-nitropyridine gives the 2-methyl product **249** (**Scheme 91**) in high yield. 3-Amino-2-chloropyridine reacts less readily and 2-chloropyridine failed to react.[135]



249

R = NO_2 90%
= NH_2 35%

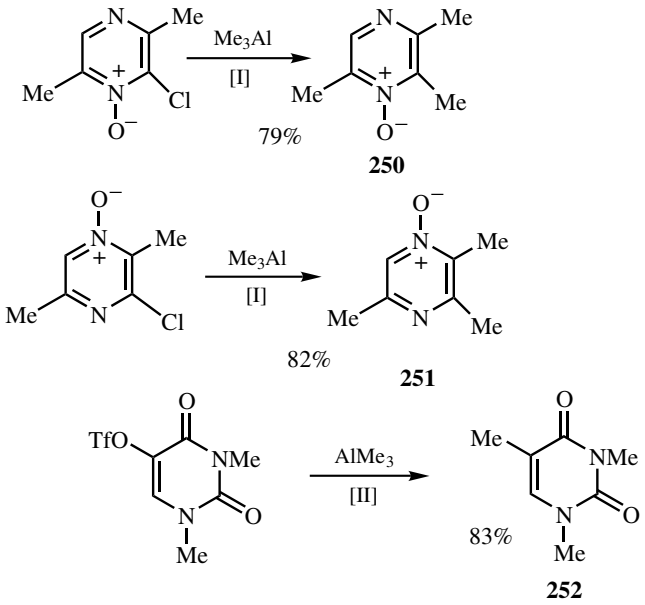
[I] 10 mol % $Pd(PPh_3)_4$, K_2CO_3, dioxane, rfx, 2 d.

Scheme 91

Aluminum Reagents. Alanes are effective donors of an alkyl group to Pd(II) after the palladium insertion into a carbon−halogen or a carbon−oxygen bond. All carbon positions in pyrazine are electrophilic. Therefore, chloropyrazines can be used as substrates for the methylation with trimethylalanes as in the preparation of the methylpyrazine *N*-oxides **250** and **251** (**Scheme 92**).[136] Triflated 5-hydroxy-1,3-dimethyluracil can be 5-methylated **252** in Pd-mediated reactions with trimethylalane.[137]

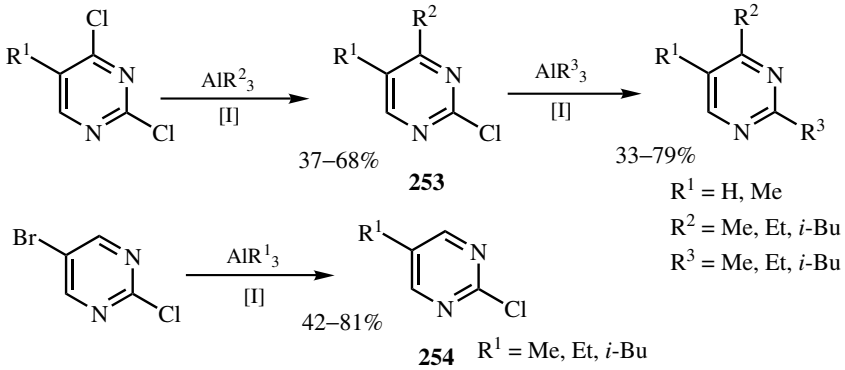
Regioselective studies of the alkylation by alanes in 2,4-dichloropyrimidines and 2,4-dichloroquinazolines show that the alkylation can be effected in a stepwise manner (**Scheme 93**). Initial alkylation is in the pyrimidine 4-position **253**. Subsequent alkylation

is in the 2-position. In 5-bromo-2-chloropyrimidine the bromine in the benzenoid 5-position is replaced by an alkyl group **254** in preference to the chloride in the electrophilic 2-position. 2,4-Dichloroquinazoline is monoalkylated in the 4-position **255**. This corresponds to the reactivity pattern seen in Stille couplings with aryl and alkenyl reagents. With triethyl- and triisobutylalane, alkylation conditions may also give some by-products due to reductive elimination of halogen. Selectivity for monosubstitution in 6-bromo-2,4-dichloroquinazoline **256** was not fully achieved. The main product was formed by substitution of the chlorine in the 4-position, the minor product from substitution of the 6-bromo substituent. The products were separated by chromatography, and each isomer was reacted separately with additional amounts of the same, or a different, alane to give the peralkylated products **257**.[138],[139]

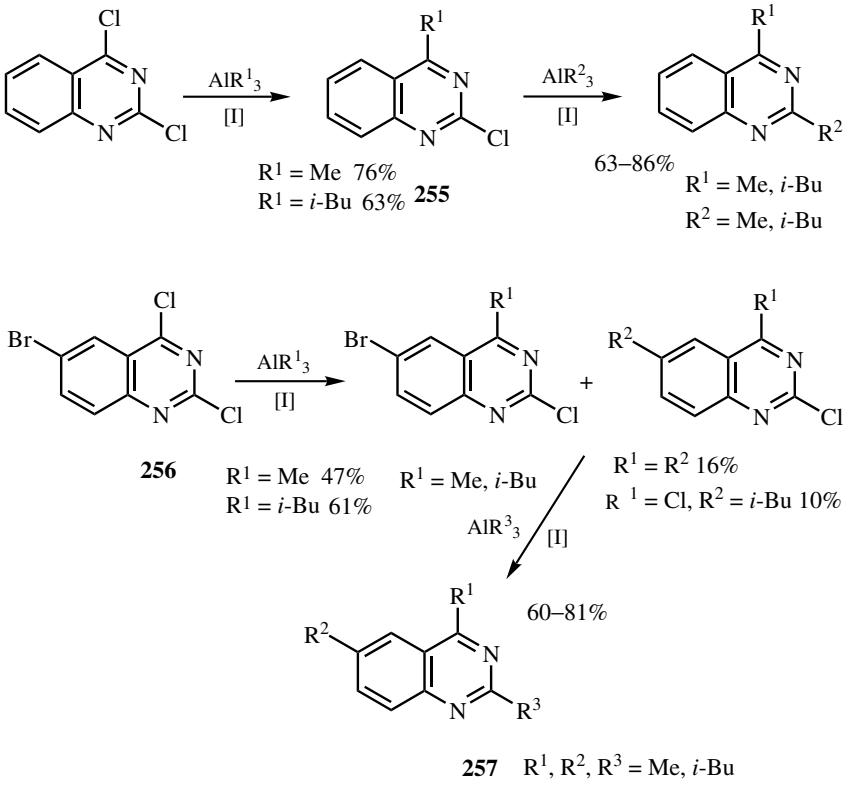


[I] 5 mol % $Pd(PPh_3)_4$, dioxane, hexane, rfx, 2 h; [II] 5 mol % $Pd(PPh_3)_4$, THF, rfx, 3 h.

Scheme 92



Scheme 93 (*Continued*)



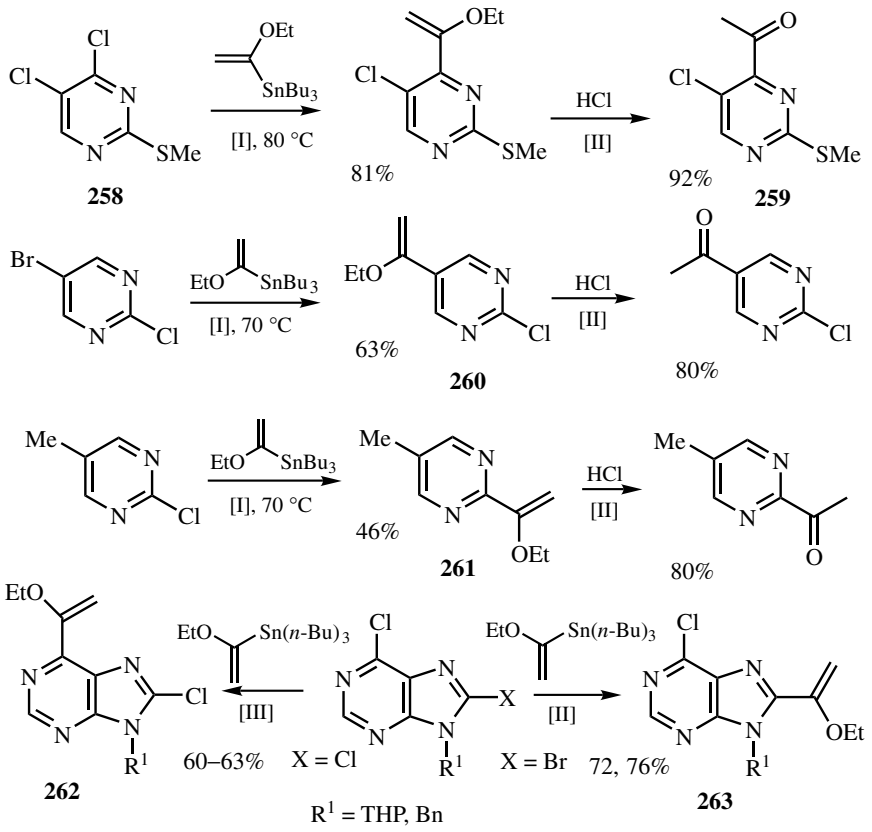
[I] 7 mol % $Pd(PPh_3)_4$, THF or DCE, rfx, 24 h.

Scheme 93 (*Continued*)

D.ii.e. *Carbonylation, Acylation, and Related Reactions*

Vinyl Ethers. α-Stannylated enol ethers provide a general and convenient substrate for introduction of acyl groups into azines (**Scheme 94**). The stannanes are available from enol ethers by α-lithiation and quenching with trialkylstannyl chloride. Mild acid hydrolysis of the α-pyrimidinylethenyl ethers yields the acyl-substituted pyrimidines such as the methyl pyrimidinyl ketone **259**. The masked acyl group is introduced into the electrophilic 4-position in the 4,5-dichloro derivative **258**. In 5-bromo-2-chloropyrimidine, chemoselectivity leads to a masked acyl group in the 5-position **260**. When the 5-substituent in the latter example is a methyl group, the masked acylation is in the 2-position **261**. The vinyl ethers are cleaved to the respective ketones by mild acid hydrolysis.[117] The same concept has successfully been applied to reactions in purines. In 6,8-dichloropurines monoselective coupling can be effected in the more electrophilic 6-position **262**. When the 8-substituent is a bromine, the order of reactivity is changed, and the initial substitution is in the 8-position **263**.[101]

Ketones can be prepared from 5-carbonyl chlorides using the Sn–Pd methodology (**Scheme 95**). The 5-(2-pyrrolocarbonyl)pyrimidine **264** is available from pyrimidine-5-carbonyl chloride in a Pd-catalyzed reaction with the corresponding 2-pyrrolostannane. The catalyst was ligated to triphenylarsine since the complex with triphenylphosphine



[I] 2 mol % $Cl_2Pd(PPh_3)_2$, DMF, 4–15 h; [II] H_2O/acetone, HCl; [III] 5 + 2.5 mol % $Cl_2Pd(PPh_3)_2$, DCE, 60 °C, 20–24 h; [IV] 5 mol % $Pd[P(2\text{-furyl}])_3]_4$, DMF, 70 °C, 7–9 h.

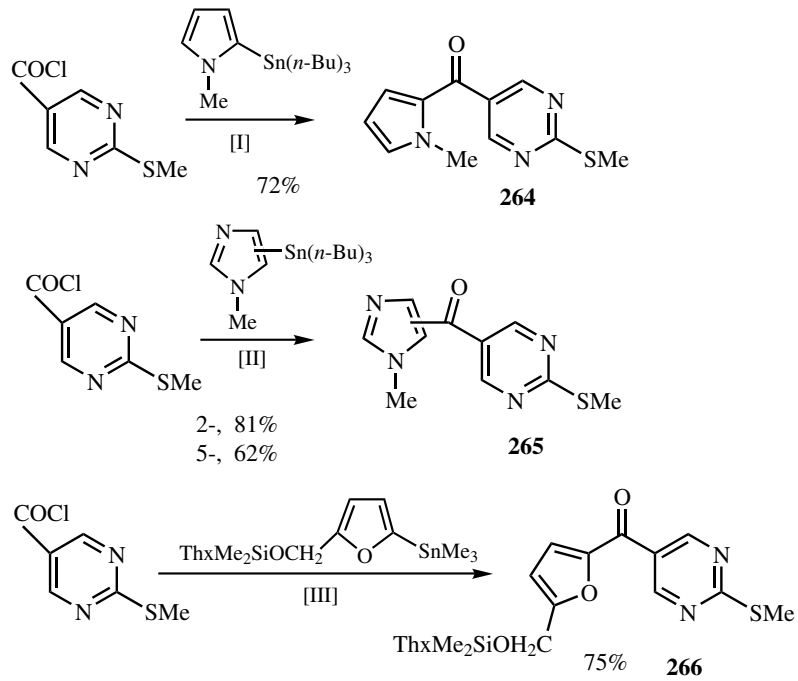
Scheme 94

was not active enough for a satisfactory conversion in this reaction. In the preparation of the imidazolyl ketones **265**, the reactions were best effected without catalyst.[95] The same approach has been used for the synthesis of the 5-pyrimidinyl 2-furyl ketone **266**.[140]

Pyridazine-3-carboxylic acids as methyl esters **267** have been prepared by methyloxycarbonylation of 3-pyridazinyl triflates in methanol using $Pd(OAc)_2$ and 1,1-bis (diphenylphosphino)ferrocene as the catalyst system together with carbon monoxide at atmospheric pressure in methanol (**Scheme 96**).[141]

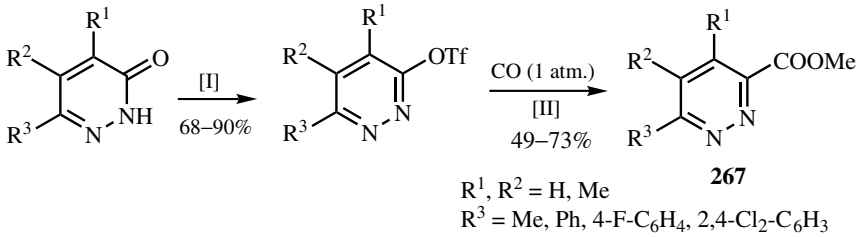
In the carbonylation of 4-trifloxy-9-SEM-β-carboline, the reaction, when effected under pressure, proceeds to furnish the ester or the carbamide products **268** in high yields.[112]

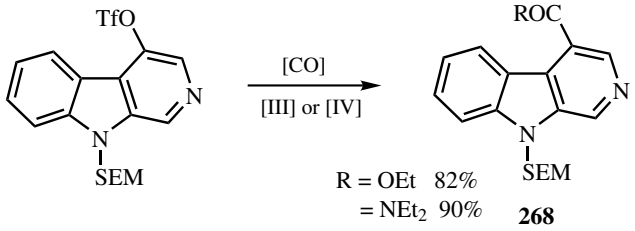
Cyanides. Zinc cyanide is a good and convenient reagent for the introduction of a cyano group by palladium-mediated coupling reactions (**Scheme 97**). 6-Triflyloxy-4(3*H*)-pyrimidinone **269** with zinc cyanide gives the corresponding 4-cyano derivative.[115] In halopurines Pd-catalyzed coupling with zinc cyanide has been used to introduce cyano groups into the purine 2- and 6-positions as shown for structures **270** and **271**. Silyl *O*-protection was advantageous in the coupling between the cyanide and



[I] 4 mol % $Pd(dba)_3CHCl_3$, $AsPh_3$, THF, r.t., 7 h; [II] THF, −78 °C to r.t., 24 h; [III] 7 mol % $Cl_2Pd(PPh_3)_2$, THF, rfx, 30 min.

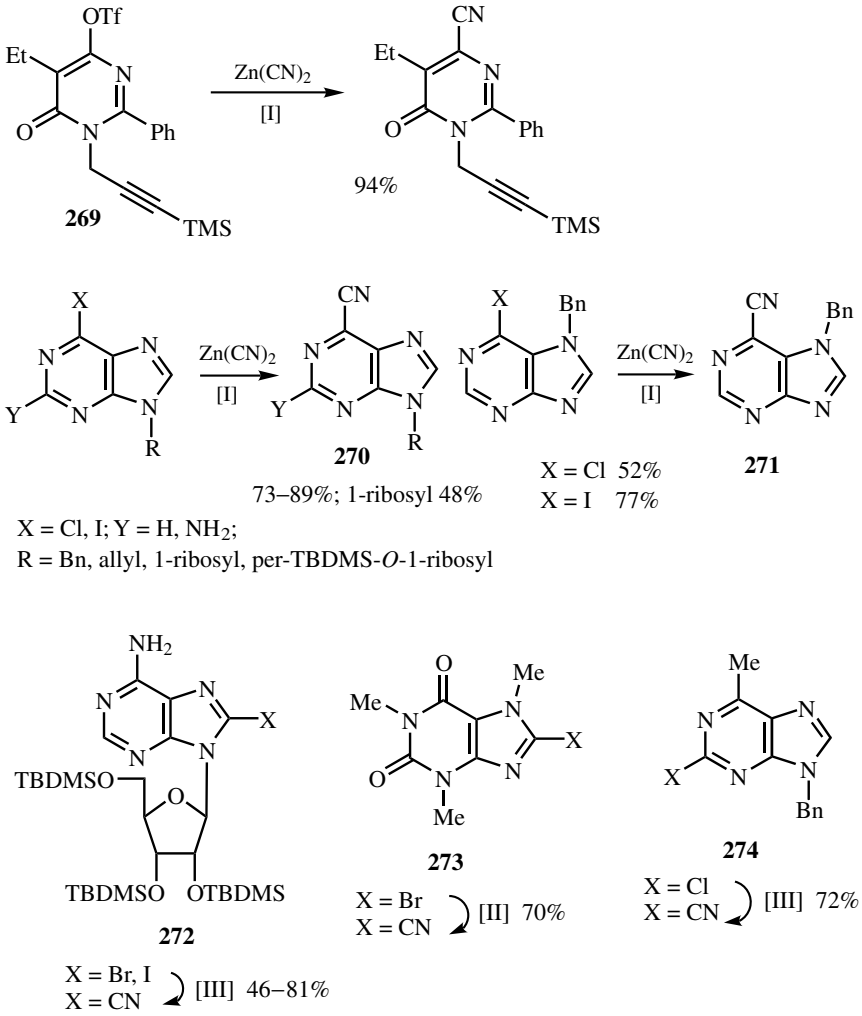
Scheme 95





[I] Tf_2O, pyridine, r.t. , 6 h; [II] 3 mol % $Pd(OAc)_2$, dppf, TEA, MeOH, DMF, 50 °C, 12 h; [III] 10 mol % $Pd(OAc)_2$, dppp, CO 100 psi, TEA, EtOH, DMF, 100 °C, 6 h; [IV] 10 mol % $Pd(OAc)_2$, dppp, CO 100 psi, TEA, $NHEt_2$, DMF, 100 °C, 10 h.

Scheme 96



[I] $Pd(PPh_3)_4$, DMF, no further details; [II] 7 mol % $Pd(PPh_3)_4$, NMP, 90 °C, 20 h;

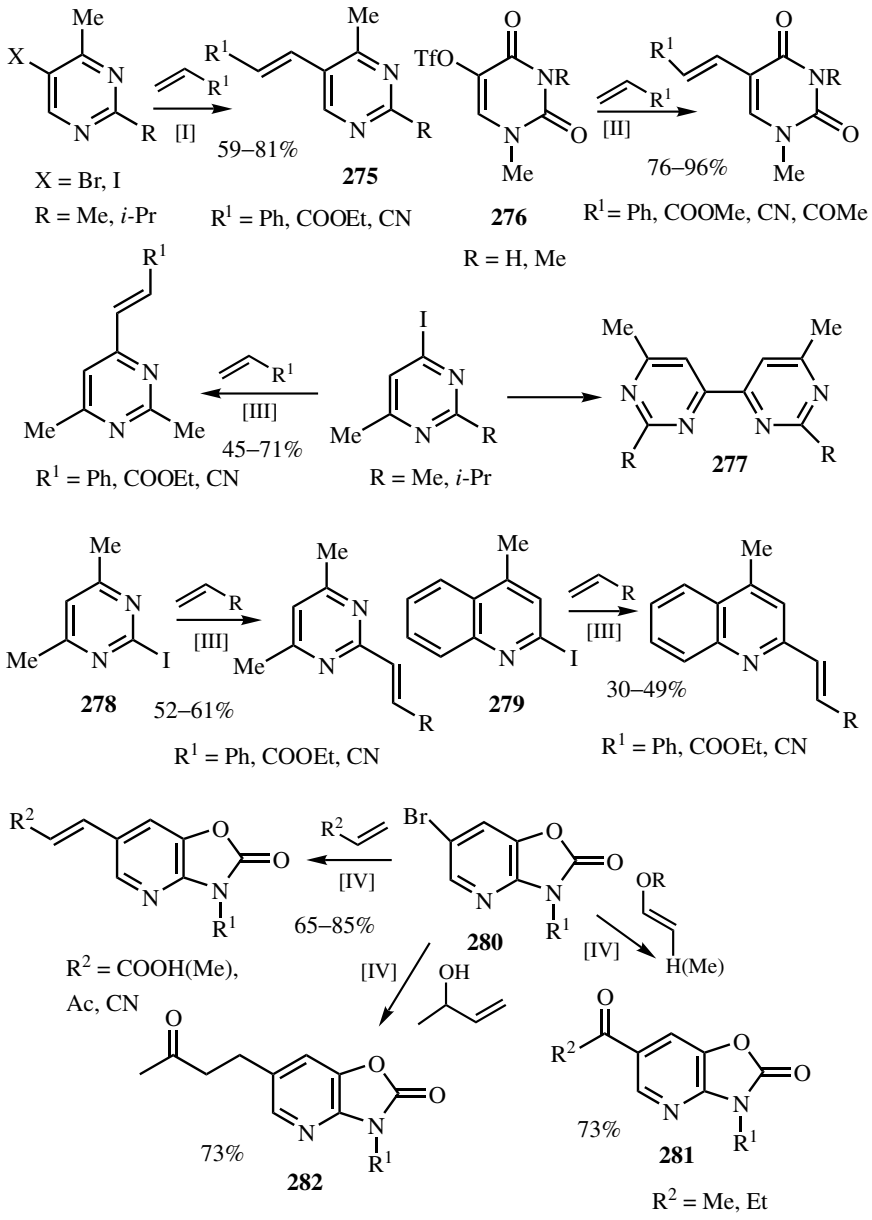
[III] 7 mol % $Pd[P(2\text{-furyl})_3]_4$, NMP, 90 °C, 20 h.

Scheme 97

the 8-halogenonucleoside **272**. Additional examples show coupling into the 8-position **273** and into the 2-position **274**. Pronounced ligand effects were observed. In most cases triphenylphosphine was the best ligand but was replaced with tris(2-furyl)phosphine when the reaction with the former ligand failed.[142]

D.ii.f. *Heck Reaction*

Acyclic Reagents. The alkenylation protocol between styrene, ethyl acrylate, or acrylonitrile and a 5-bromo- and 5-iodopyrimidine leads to coupling products **275** (**Scheme 98**).[143] Methoxy-, methylthio-, and amino groups are tolerated.[127],[144] A triflyloxy substituent may replace the iodo substituent. 1-Methyl- and 1,3-dimethyluracil-5-yl triflate



[I] 2 mol % $Pd(OAc)_2$, PPh_3, NEt_3, 120–150 °C; [II] 2 mol % $PdCl_2$, PPh_3, NEt_3, DMF, 60–70 °C; [III] 2 mol % $Pd(OAc)_2$, NEt_3, 80–100 °C, 12–36 h; [IV] 1 mol % $Pd(OAc)_2$, 4 mol % P(*o*-tol)$_3$, NEt_3, DMF, 130 °C, 3 h.

Scheme 98

276 are alkenylated by styrene, acrylonitrile, methyl acrylate, or methyl vinyl ketone.[145] Formation of 4,4′-bipyrimidines **277** is a major pathway from 4-iodopyrimidines under the conditions used to effect the Heck reaction. In the absence of alkenes, the homocoupling is almost quantitative.[143],[146] With 2-iodopyrimidines **278** moderate yields of 2-alkenylated pyrimidines were obtained. Similar coupling can be effected in 2-iodo-4-methylquinoline **279**. The regioisomeric 4-iodo-2-methylquinoline was less reactive.[147] In 6-bromoxazolo-[4,5-*b*]pyridin-2(3*H*)-ones **280**, alkenylation in the 6-position proceeds in moderate to high yields. With vinyl ethers, the bond-forming reaction is at the α-carbon eventually leading to acylation **281**. An allylic alcohol gives the corresponding ketonyl side-chain product **282**.[148]

Cyclic Reagents. In the Heck coupling between 2,3-dihydrofuran and 5-iodouracil the bond formation is at the α-vinyl carbon of the cyclic vinyl ether. An almost 1:1 mixture of double bond isomers **283** and **284** resulted when 2 equiv of triphenylphosphine per palladium diacetate was used (**Scheme 99**). Triphenylarsine is the better ligand. Similar conditions were used for the coupling between 5-iodouracil and a ribofuranoid glycal to yield the *C*-5-nucleoside precursor **285**. The Heck coupling was both regio- and stereospecific.[82] In closely related reactions the functionalized iodopyrazine **286** was used in a regio- and stereospecific synthesis of pyrazine *C*-nucleosides with β-configuration **287**. In these reactions only trace amounts of the α-products were seen. The silyl ether product readily suffers hydrolysis and was converted to its ketone **288** on treatment with tetrabutylammonium fluoride.[149] Heck coupling between 2,6-dichloro-3-iodoimidazo[1,2-*a*]pyridine **289** and 2,3-dihydrofuran has been used to prepare intermediates **290** for *C*-nucleosides. In the reaction sequence, initial iodination was effected by NIS in the imidazole ring, rather than in the π-deficient pyridine moiety. Silver salts were added to the coupling mixture in a DMF solution to reduce the tendency for double bond migration, in which case the 2,5-dihydrofuran derivative **290** was obtained.[150]

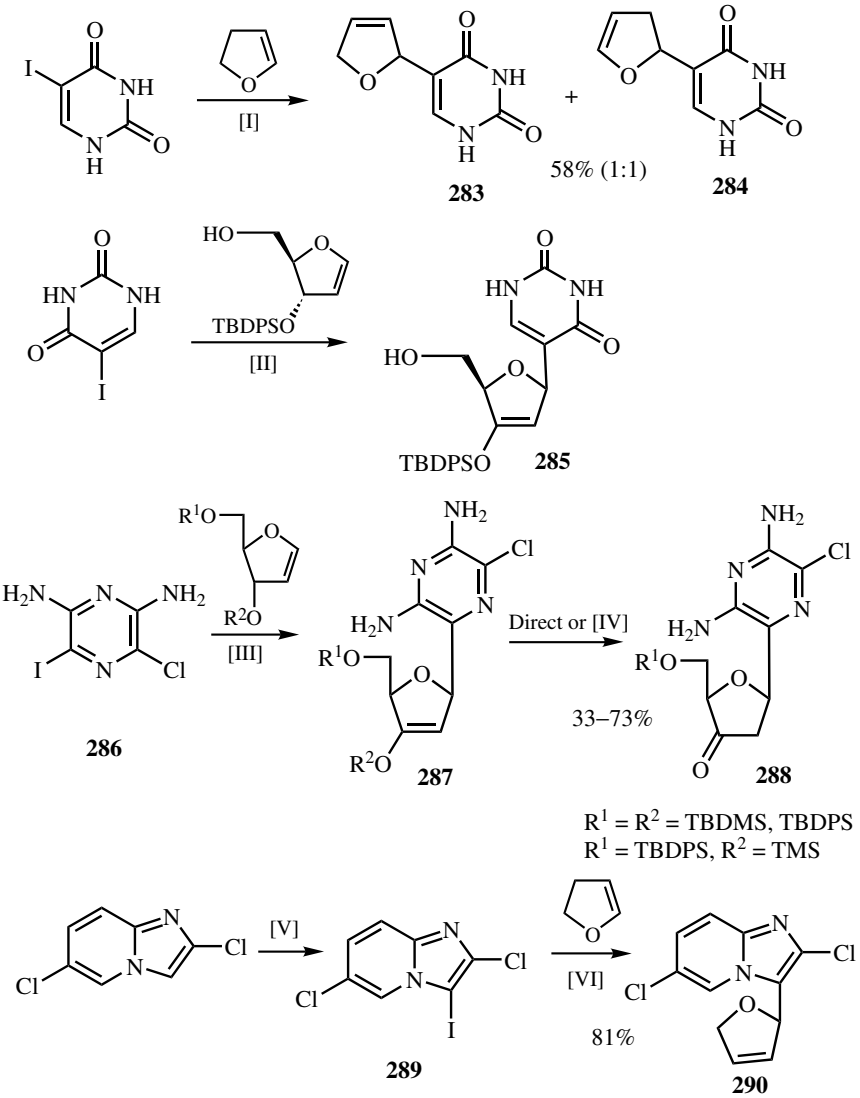
D.ii.g. *Annulation*

Heck Annulation. Polyheterocylic systems such as pyrido[2′,3′-*d*′]pyridazino[2,3-*a*]indoles **291** are available by Heck annulation reactions using nicotinyl-indole substrates (**Scheme 100**).[151]

Cyclization of iodopyridinyl allyl ethers derived fom dihalopyridines and sodium allylic oxides leads to formation of furo[2,3-*b*]pyridines **292**, furo[3,2-*c*]pyridines **293**, and furo[2,3-*c*]pyridines **294** by a Heck mode of reaction (**Scheme 101**). In the reaction sequences, the initial step in the preparation of iodopyridine allyl ethers involves regioselective lithiation of 3-fluoro, 2-fluoro-, and 4-chloropyridines with LDA. Subsequently, the lithiated species are treated with iodine as electrophile. A variety of iodopyridinyl ethers have been prepared from dihalopyridines and sodium allylic oxides and subjected to the Pd-catalyzed cyclization reactions with formation of the furoannulated pyridine products. When the allyl groups carry a 2-substituent as in structure **295**, hydridopalladium elimination is prevented. Instead, sodium formate reductive elimination of the palladium substituent gives the product **296**. The isomeric structures **297** and **298** are available similarly.[152]

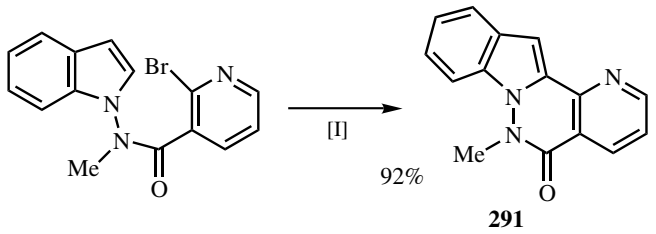
Annulation Via Heterosubstituent. In the alkynylation of 5-iodo-1-methyluracil under Sonogashira conditions (**Scheme 102**) a minor product (9%) from the reaction was furo[2,3-*d*]pyrimidin-6-one **299**. The latter arises from the initial coupling product by a

subsequent cyclization reaction. The cyclization was demonstrated by heating the alkynylated product with CuI/NEt_3/MeOH, which gave a 92% yield of the furopyrimidine **299**.[125] This reaction provides a method for the preparation of furo[2,3-*d*]pyrimidines. The same reaction has been found useful for carbosubstitution in nucleosides. Thus, a Sonogashira coupling of 5-iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine with trimethylsilylacetylene gave the 5-alkynylated product **300**, which was cyclized to the furo[2,3-*d*]pyrimidin-6-one nucleosides **301** as the major product.[125] 4-Arylamino-8-iodoquinoline derivatives **302** react with propargyl alcohol under Sonogashira conditions



[I] 10 mol % $Pd(OAc)_2$, 20 mol % $AsPh_3$, $(n\text{-}Bu)_4NCl$, DMF, 50 °C, 3 h; [II] as [I] except for 60 °C, 15 h; [III] $Pd(OAc)_2$, $AsPh_3$, NEt_3, MeCN, 50 °C; [IV] TBAF, THF, −20 °C; [V] NIS, $CHCl_3$; [VI] 10 mol % $Pd(OAc)_2$, 20 mol % $AsPh_3$, NEt_3, Ag_2CO_3, 45 °C.

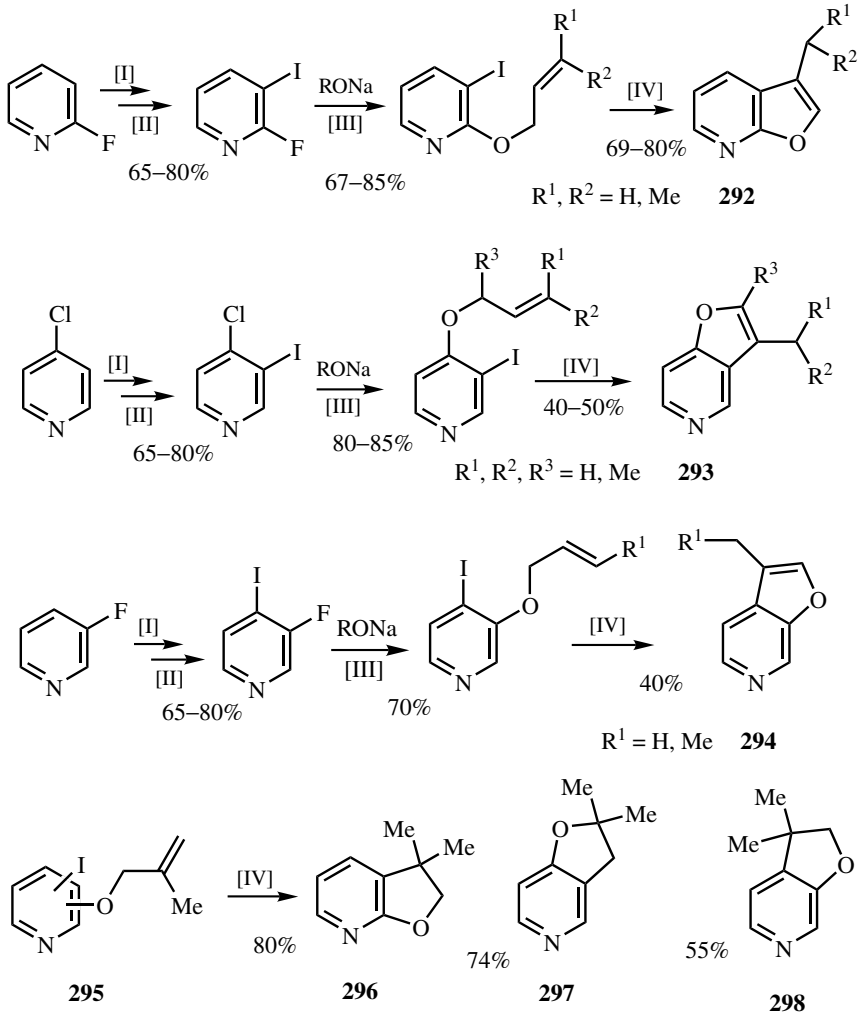
Scheme 99



291

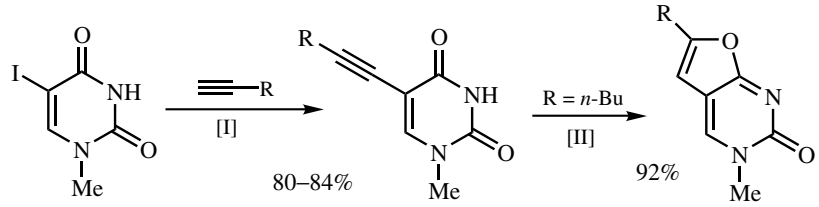
[I] 10 mol % $Pd(OAc)_2$, PPh_3, $(n\text{-}Bu)_4NBr$, K_2CO_3, DMF, 120 °C, 2 h.

Scheme 100

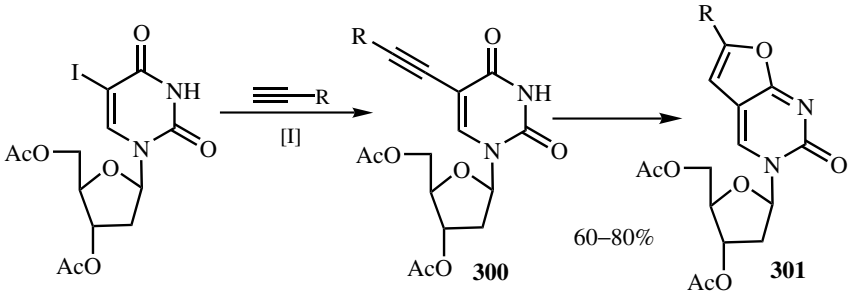


[I] LDA, THF, −78 °C; [II] I_2, [III] RONa, THF, rfx, 3–4 h; [IV] 2.5 mol % $Pd(OAc)_2$, $(n\text{-}Bu)_4NCl$, K_2CO_3, HCOONa, DMF, 100 °C, 3–4 h.

Scheme 101

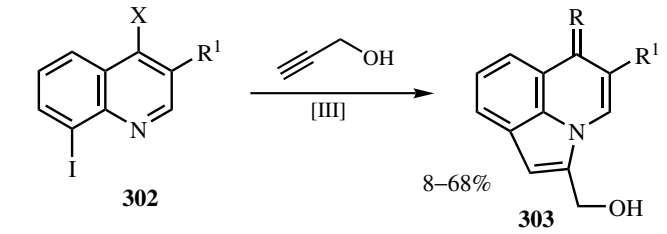


R = *n*-Bu, CH_2CH_2O-*p*-toluene **299**



300 **301**

R = $SiMe_3$, *n*-Bu, EtOOC, 4-MeC_6H_4



302 **303**

X = OH, NHPh, NHC_6H_4-2-Me
R^1 = H, CO(*n*-Pr), COOEt

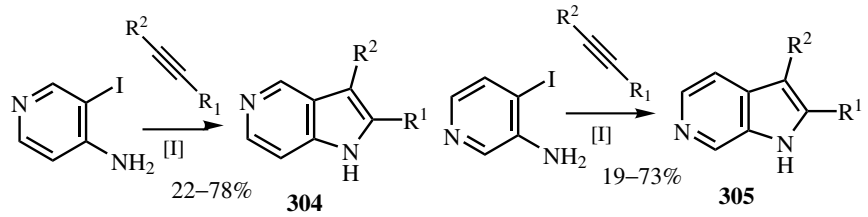
R = O, NPh, NC_6H_4-2-Me

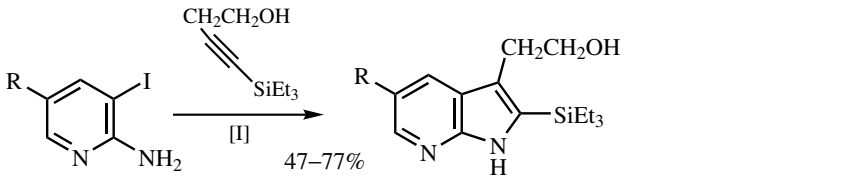
[I] 1 mol % $Cl_2Pd(PPh_3)_2$, CuI, NEt_3, 50 °C, 2 h; [II] CuI, NEt_3, MeOH, rfx, 4 h;
[III] 2 mol % $Pd(PPh_3)_4$, CuI, NEt_3, toluene, r.t., 48 h.

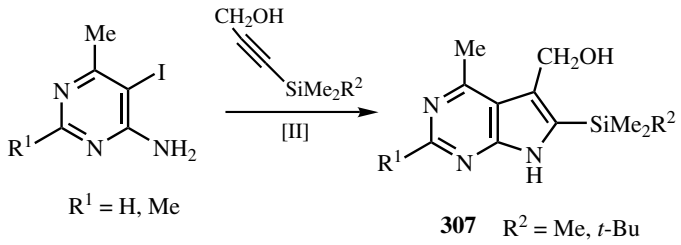
Scheme 102

and triethylamine as base to yield 6-imino-substituted pyrrolo[3,2-*i*]quinolines **303**. In this reaction the quinoline nitrogen acts as a nucleophile, and adds to the reaction intermediate resulting in formation of the new pyrroloannulated ring.[153]

Internal Alkynes. Several applications of the Larock synthesis of indoles have been published where heterocycles are used as substrate.[56],[154] In the Larock method for indol construction, Pd-catalyzed heteroannulation of internal alkynes using *ortho*-iodoanilines are used. Similarly, Pd-catalyzed heteroannulation of internal alkynes using *ortho*-amino-iodopyridine substrates produces azaindoles (**Scheme 103**). The method provides a convenient access to a structurally diverse range of 5-, 6-, and 7-azaindoles, **304**, **305**, and





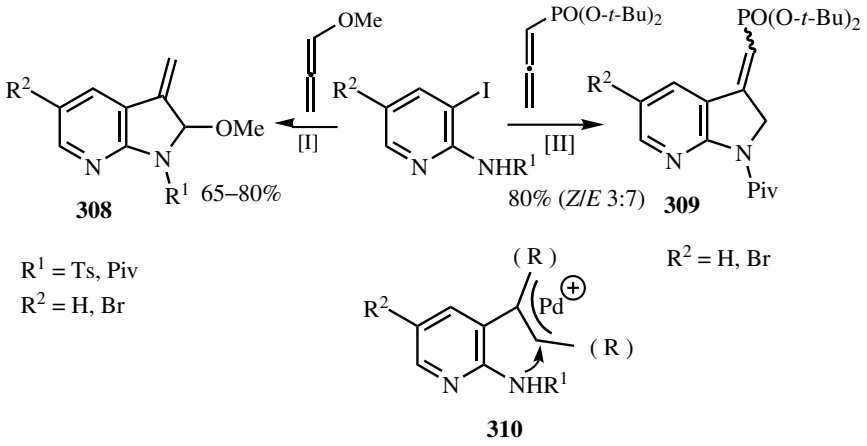


[I] 5 mol % $Cl_2Pd(dppf)$, LiCl, Na_2CO_3, DMF, 100 °C, 15 h; [II] 5 mol % $Pd(OAc)_2$, PPh_3, $(n\text{-}Bu)_4NCl$, NEt_3, DMF, 90–100 °C, 19–32 h.

Scheme 103

306, respectively. The heteroannulation of silylalkynes is highly regioselective, providing only the one isomer with the bulky silyl group next to the indole nitrogen.[155] Another recent publication describes the preparation of a closely related series of 2,3-disubstituted 7-azaindoles.[156] Preparation of diazaindoles in the form of pyrrolo[2,3-*d*]pyrimidines **307** can be effected in a similar manner.[157]

The Larock method for annulation between vicinal iodo-arylamines and 1,2-dienes in the preparation of indoles can be adapted for preparation of azaindoles using corresponding azine substrates. Thus, substituted-3*H*-pyrrolo[2,3-*b*]pyridin-3-ones can be prepared from 2-amino-3-iodopyridine derivatives by a palladium carboannulation process with allenic compounds (**Scheme 104**). The bicyclic products, the methylene derivatives **308**, and the alkylidenes **309** can be oxidatively cleaved with ketone formation. The reaction may proceed by formation of a pyridinylpalladium complex followed by the π-allyl complexation of allenic derivatives **310**. Since the polar substituents on terminal carbons of the π-allyl system influence the regiochemistry of the reactions, nucleophilic attack of the nitrogen atom on the most electron-deficient carbon atom of the π-allyl system affords either of the



Scheme 104

structures. The methoxy group in the methoxyallene stabilizes the most electrophilic carbon, C-1 in this case. With allenic phosphonate, however, the C-3 atom is the more positive, due to the electronic effects of the phosphonate group and the vinylphosphonate **309** is formed.[158]

REFERENCES

[1] V. N. Kalinin, *Synthesis*, **1992**, 413–432.

[2] K. Undheim and T. Benneche, *Adv. Heterocyclic Chem.*, **1995**, *62*, 305–418.

[3] K. Undheim and T. Benneche, in *Comprehensive. Heterocyclic Chemistry II*, A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds. (A. J. Boulton, Vol. Ed.), **1996**, *Vol*. 6, 93–231.

[4] R. L. Hudkins, J. L. Diebold, and F. D. Marsh, *J. Org. Chem.*, **1995**, *60*, 6218.

[5] G. Palmisano and M. Santagostino, *Helv. Chim. Acta*, **1993**, *76*, 2356.

[6] M. Alvarez, D. Fernández, and J. A. Joule, *Synthesis*, **1999**, 615.

[7] L. Brandsma, S. F. Vasilevsky, and H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer, Berlin, **1998**, 259–275.

[8] D. Prim and G. Kirsch, *J Chem Soc. Perkin Trans. 1*, **1994**, 2603.

[9] M. Amat, S. Hadida, G. Pshenichnyi, and J. Bosch, *J. Org. Chem.*, **1997**, 3158.

[10] T. Sakamoto, Y. Kondo, N. Takazawa, and H. Yamanaka, *J. Chem. Soc. Perkin Trans. 1*, **1996**, 1vz927.

[11] W. J. Thompson and J. Gaudino, *J. Org. Chem.*, **1984**, *49*, 5237.

[12] S. Gronowitz, V. Bobosik, and K. Lawitz, *Chem. Scr.*, **1984**, *23*, 120.

[13] Y. Yang, *Synth. Commun.*, **1989**, *19*, 1001.

[14] S. Gronowitz, A.-B. Hörnfeldt, and Y.-H. Yang, *Chem. Scr.*, **1986**, *26*, 383.

[15] A. Alvarez, A. Guzman, A. Ruiz, E. Velarde, and J. M. Muchowski, *J. Org. Chem.*, **1992**, *57*, 1653.

[16] I. Kawasaki, H. Katsuma, Y. Nakayama, M. Yamashita, and S. Ohta, *Heterocycles*, **1998**, *48*, 1887.

[17] C. N. Johnson, G. Stemp, N. Anand, S. C. Stephen, and T. Gallagher, *Synlett*, **1998**, 1025.

[18] M. Ishikura, Y. Matsuzaki, and I. Agata, *Heterocycles*, **1997**, *45*, 2309.

[19] Z. Z. Song, M. S. Ho, and H. N. C. Wong, *J. Org. Chem.*, **1994**, *59*, 3917.
[20] O. Meth-Cohn and H. Jiang, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 3737.
[21] Y. Yang and H. N. C. Wong, *J. Chem. Soc. Chem. Commun.*, **1992**, 656.
[22] M. Ishikura, Y. Matsuzaki, I. Agata, and N. Katagiri, *Tetrahedron*, **1998**, *54*, 13929.
[23] A. G. Birchler, F. Liu, and S. L. Liebeskind, *J. Org. Chem.*, **1994**, *59*, 7737.
[24] L. S. Liebeskind and J. Wang, *J. Org. Chem.*, **1993**, *58*, 3550.
[25] Y. Yang and H. N. C. Wong, *Tetrahedron*, **1994**, *50*, 9583.
[26] X.-S. Ye and H. N. C. Wong, *J. Org. Chem.*, **1997**, *62*, 1940.
[27] M. M. Faul and L. L. Winneroski, *Tetrahedron Lett.*, **1997**, *38*, 4749.
[28] E. D. Edstrom and Y. Wei, *J. Org. Chem.*, **1993**, *58*, 403.
[29] E. D. Edstrom and Y. Wei, *J. Org. Chem.*, **1994**, *59*, 6902.
[30] R. Rai, K. B. Aubrecht, and D. B. Collum, *Tetrahedron Lett.*, **1995**, *36*, 3111.
[31] E. Negishi, T. Takahashi, and A. O. King, *Org. Synth.*, **1993**, *C8*, 430.
[32] X.-S. Ye, P. Yu, and H. N. C. Wong, *Liebigs Ann./Recl.*, **1997**, 459.
[33] J. P. Wolfe, R. A. Singer, B. H. Yang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **1999**, *121*, 9550.
[34] M. Ishikura, M. Kamada, and M. Terashima, *Synthesis*, **1984**, 936.
[35] J. Hassan, L. Lavenot, C. Gozzi, and L. Lemaire, *Tetrahedron Lett.*, **1999**, *40*, 857.
[36] T. Choshi, T. Sada, H. Fujimoto, C. Nagayama, E. Sugino, and S. Hibino, *J. Org. Chem.*, **1997**, *62*, 2535.
[37] L. Brandsma, S. F. Vasilevsky, and H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer, Berlin, **1998**, 259–275.
[38] T. Sakamoto, T. Nagano, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **1988**, *36*, 2248.
[39] T. X. Neeman and G. M. Whitesides, *J. Org. Chem.*, **1988**, *53*, 2489.
[40] E. Negishi, C. Xu, Z. Tan, and M. Kotora, *Heterocycles*, **1997**, *46*, 209.
[41] K. Hirota, Y. Kitade, Y. Kanbe, and Y. Maki, *J. Org. Chem.*, **1992**, *57*, 5268.
[42] E. D. Edstrom and T. Yu, *Tetrahedron Lett.*, **1994**, *35*, 6985.
[43] J. M. Herbert and A. H. McNeill, *Tetrahedron Lett.*, **1998**, *39*, 2421.
[44] C. Gozzi, L. Lavenot, K. Ilg, V. Penalva, and M. Lemaire, *Tetrahedron Lett.*, **1997**, *38*, 8867.
[45] Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita, and A. Ohta, *Heterocycles*, **1992**, *33*, 257.
[46] I. Basnak, S. Takatori, and R. T. Walker, *Tetrahedron Lett.*, **1997**, *38*, 4869.
[47] Z. Z. Song and H. N. C. Wong, *Liebigs Ann. Chem.*, **1994**, 29.
[48] G. W. Gribble and S. C. Conway, *Synth. Commun.*, **1992**, *22*, 2129.
[49] E. Desarbre and J.-Y. Mérour, *Heterocycles*, **1995**, *41*, 1987.
[50] R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam, and T. Worakun, *Tetrahedron*, **1990**, *46*, 4003.
[51] T. Sakamoto, Y. Kondo, M. Uchiyama, and H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1941.
[52] J. E. Macor, D. H. Blank, R. J. Post, and K. Ryan, *Tetrahedron Lett.*, **1992**, *33*, 8011.
[53] R. J. Sundberg and W. J. Pitts, *J. Org. Chem.*, **1991**, *56*, 3048.
[54] D. Wensbo, U. Annby, and S. Gronowitz, *Tetrahedron*, **1995**, *51*, 10323.
[55] R. Grigg, P. Fretwell, C. Meerholtz, and V. Sridharan, *Tetrahedron*, **1994**, *50*, 359.
[56] R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, **1991**, *113*, 6689.

[57] D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, S. Gronowitz, and L. A. Cohen, *Tetrahedron Lett.*, **1993**, *34*, 2823.

[58] A. Dondoni, G. Fantin, M. Fogagnoli, A. Medici, and P. Pedrini, *Synthesis*, **1987**, 693.

[59] M. Kosugi, M. Koshiba, A. Atoh, H. Sano, and T. Migita, *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 677.

[60] K. V. Gothelf and K. B. G. Torssell, *Acta Chem. Scand.*, **1994**, *48*, 61.

[61] D. Uchiyama, M. Yabe, H. Kameyama, T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, **1996**, *43*, 1301.

[62] J. Elguero, C. Jaramillo, and C. Pardo, *Synthesis*, **1997**, 563.

[63] B. A. Anderson and N. K. Harn, *Synthesis*, **1996**, 583.

[64] B. A. Anderson, L. M. Becke, R. N. Booher, M. E. Flaugh, N. K. Harn, T. J. Kress, D. L. Varie, and J. P. Wepsiec, *J. Org. Chem.*, **1997**, *62*, 8634.

[65] J. Felding, P. Uhlmann, J. Kristensen, P. Vedso, and M. Begtrup, *Synthesis*, **1998**, 1181.

[66] M. D. Cliff and S. G. Pyne, *Tetrahedron*, **1996**, *52*, 13703.

[67] E. Crowe, F. Hossner, and M. J. Hughes, *Tetrahedron*, **1995**, *51*, 8889.

[68] D. Wang and J. Haseltine, *J. Heterocycl. Chem.*, **1994**, *31*, 1637.

[69] J. Ozola, T. Persson, S. Gronowitz, and A.-B. Hørnfeldt, *J. Heterocycl. Chem*., **1995**, *32*, 863.

[70] Y. Hanasaki, *Heterocycles*, **1996**, *43*, 2435.

[71] F. Clerici, E. Erba, M. L. Gelm, and M. Valle, *Tetrahedron*, **1997**, *53*, 15859.

[72] M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, **1985**, *26*, 5997.

[73] J. Ezquerra, C. Lamas, A. Pastor, J. L. Garcia-Navio, and J. J. Vaquero, *Tetrahedron*, **1997**, *53*, 12755.

[74] K. Y. Yi and S.-E. Yoo, *Tetrahedron Lett.*, **1995**, *36*, 1679.

[75] M. D. Cliff and S. G. Pyne, *Synthesis*, **1994**, 681.

[76] N. Minakawa, T. Sasaki, and A. Matsuda, *Tetrahedron*, **1998**, *54*, 13517.

[77] T. Sakamoto, H. Nagata, Y. Kondo, M. Shiraiwa, and H. Yamanaka, *Chem. Pharm. Bull.*, **1987**, *35*, 823.

[78] H. Yamanaka, M. Shiraiwa, E. Yamamoto, and T. Sakamoto, *Chem. Pharm. Bull.*, **1981**, *29*, 3543.

[79] E. V. Tretyakov, D. W. Knight, and S. F. Vasilefsky, *J. Chem. Soc. Perkin Trans. I*, **1999**, 3713.

[80] E. C. Taylor and H. H. Patel, *Tetrahedron*, **1992**, *48*, 8089.

[81] T. Sakamoto, Y. Kondo, T. Suginome, S. Ohba, and H. Yamanaka, *Synthesis*, **1992**, 552.

[82] H.-C. Zhang and G. D. Daves, *J. Org. Chem.*, **1992**, *57*, 4690.

[83] A. J. Majeed, Ø. Antonsen, T. Benneche, and K. Undheim, *Tetrahedron*, **1989**, *45*, 993.

[84] J. Sandosham and K. Undheim, *Acta Chem. Scand.*, **1989**, *43*, 684.

[85] J. A. Zoltewicz and M. P. Cruskie, *J. Org. Chem.*, **1995**, *60*, 3487.

[86] F. Guillier, F. Nivoliers, A. Godard, F. Marsais, G. Queguiner, M. A. Siddiqui, and V. Snieckus, *J. Org. Chem.*, **1995**, *60*, 292.

[87] A. S. B. Prasad and P. Knochel, *Tetrahedron*, **1997**, *53*, 16711.

[88] T. Sakamoto, Y. Kondo, N. Murata, and H. Yamanaka, *Tetrahedron*, **1993**, *49*, 9713.

[89] F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais, and G. Quéguiner, *Tetrahedron*, **2000**, *56*, 1349.

[90] T. Takahashi, H. Koga, H. Sato, T. Ishizawa, and N. Taka, *Heterocycles*, **1995**, *41*, 2405.

[91] M. Ishikura, M. Kamada, T. Ohta, and M. Terashima, *Heterocycles*, **1984**, *22*, 2475.

[92] Y. Yamamoto, T. Tanaka, H. Ouchi, M. Miyakawa, and Y. Mori, *Heterocycles*, **1995**, *41*, 817.

[93] M.-C. Viaud, P. Jamoneau, M.-L. Baudin, L. Savelon, and G. Guillaumet, *Tetrahedron*, **1997**, *53*, 5159.

[94] J. Sandosham and K. Undheim, *Tetrahedron*, **1994**, *50*, 275.
[95] K. Gaare, T. Repstad, T. Benneche, and K. Undheim, *Acta Chem. Scand.*, **1993**, *47*, 57.
[96] J. Arukwe, T. Benneche, and K. Undheim, *J. Chem. Soc. Perkin Trans. 1*, **1989**, 225.
[97] D. Peters, A.-B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, **1990**, *27*, 2165.
[98] B. Danieli, G. Lesma, M. Martinelli, D. Passarella, I. Peretto, and A. Silvani, *Tetrahedron*, **1998**, *54*, 14081.
[99] T. L. Draper and T. R. Bailey, *J. Org. Chem.*, **1995**, *60*, 748.
[100] Y. Yamamoto, T. Seko, and H. Nemoto, *J. Org. Chem.*, **1989**, *54*, 4734.
[101] J. M. J. Nolsøe, L.-L. Gundersen, and F. Rise, *Acta Chem. Scand.*, **1999**, *53*, 366.
[102] J. Sandosham and K. Undheim, *Heterocycles*, **1994**, *37*, 501.
[103] J. Sandosham, K. Undheim, and F. Rise, *Heterocycles*, **1993**, *35*, 235.
[104] K. Undheim and T. Benneche, *Acta Chem. Scand.*, **1993**, *47*, 102.
[105] S. Gronowitz, A.-B. Hörnfeldt, V. Kristjansson, and T. Musil, *Chem. Scr.*, **1986**, *26*, 305.
[106] K. Jones, M. Keenan, and F. Hibbert, *Synlett*, **1996**, 509.
[107] D. Janietz and M. Bauer, *Synthesis*, **1993**, 33.
[108] M. A. Ciufolini, J. W. Mitchell, and F. Roschangar, *Tetrahedron Lett.*, **1996**, *37*, 8281.
[109] S. Grivas and S. Lindstrom, *J Heterocycl. Chem.*, **1995**, *32*, 467.
[110] J. W. Goodby, M. Hird, R. A. Lewis, and K. J. Toyne, *J. Chem. Soc. Chem. Commun.*, **1996**, 2719.
[111] J. A. Zoltewicz, M. P. Cruskie, and C. D. Dill, *J. Org. Chem.*, **1995**, *60*, 264.
[112] C. A. Busacca, M. C. Eriksson, Y. Dong, A. S. Prokopowicz, A. M. Salvagno, and M. A. Tschantz, *J. Org. Chem.*, **1999**, *64*, 4564.
[113] J. Hassan, V. Penalva, L. Lavenot, C. Gozzi, and M. Lemaire, *Tetrahedron*, **1998**, *54*, 13793.
[114] A. Bråthe, L.-L. Gundersen, F. Rise, A. B. Eriksen, A. V. Vollsnes, and L. Wang, *Tetrahedron*, **1999**, *55*, 211.
[115] E. C. Taylor, P. Zhou, and C. M. Tice, *Tetrahedron Lett.*, **1997**, *38*, 4343.
[116] J. Sandosham, T. Benneche, B. S. Möller, and K. Undheim, *Acta Chem. Scand.*, **1988**, *B42*, 455.
[117] J. Solberg and K. Undheim, *Acta Chem. Scand.*, **1989**, *43*, 62.
[118] A. Minato, K. Suzuki, K. Tamao, and M. Kumada, *Tetrahedron Lett.*, **1984**, *25*, 83.
[119] J.-P. Gillet, R. Sauvetre, and J.-F. Normant, *Tetrahedron Lett.*, **1985**, *26*, 3999.
[120] E. Negishi, F.-T. Luo, R. Frisbee, and H. Matsushita, *Heterocycles*, **1982**, *18*, 117.
[121] I. Mangalagiu, T. Benneche, and K. Undheim, *Acta Chem. Scand.*, **1996**, *50*, 914.
[122] M. L. Falck-Pedersen and K. Undheim, *Acta Chem. Scand.*, **1998**, *52*, 1327.
[123] T. Sakamoto, M. An-Naka, Y. Kondo, T. Ardie, and H. Yamamoto, *Chem. Pharm. Bull.*, **1988**, *36*, 1890.
[124] Y. Akita, A. Inoue, and A. Ohta, *Chem. Pharm. Bull.*, **1986**, *34*, 1447.
[125] M. J. Robins and P. J. Barr, *J. Org. Chem.*, **1983**, *48*, 1954.
[126] S. A. Adah and V. Nair, *Tetrahedron*, **1997**, *53*, 6747.
[127] T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **1982**, *30*, 2410.
[128] J. Solberg and K. Undheim, *Acta Chem. Scand. Ser. B*, **1986**, *40*, 381.
[129] C. S. Kim and K. C. Russell, *J. Org. Chem.*, **1998**, *63*, 8229.
[130] J. Solberg and K. Undheim, *Acta Chem. Scand. Ser. B*, **1987**, *B41*, 712.
[131] M. C. Viaud, P. Jamoneau, L. Savelon, and G. Guillaumet, *Tetrahedron Lett.*, **1996**, *37*, 2409.
[132] T. Sakamoto, S. Nishimura, Y. Kondo, and H. Yamanaka, *Synthesis*, **1988**, 485.

[133] R. F. W. Jackson, N. Wishart, A. Wood, K. James, and M. J. Wythes, *J. Org. Chem.*, **1992**, *57*, 3397.

[134] T. Shiota and T. Yamamori, *J. Org. Chem.*, **1999**, *64*, 453.

[135] C. Niu, J. Li, T. W. Doyle, and S.-H. Chen, *Tetrahedron*, **1998**, *54*, 6311.

[136] A. Ohta, A. Inoue, K. Ohtsuka, and T. Watanabe, *Heterocycles*, **1985**, *23*, 133.

[137] K. Hirota, Y. Isobe, and Y. Maki, *J. Chem. Soc. Perkin Trans. 1*, **1989**, 2513.

[138] I. Mangalagiu, T. Benneche, and K. Undheim, *Tetrahedron Lett.*, **1996**, *37*, 1309.

[139] Q. Lu, I. Mangalagiu, T. Benneche, and K. Undheim, *Acta Chem. Scand.*, **1997**, *51*, 302.

[140] J. Arukwe and K. Undheim, *Acta Chem. Scand.*, **1991**, *45*, 914.

[141] M. Rohr, D. Toussaint, S. Chayer, A. Mann, J. Suffert, and C. G. Wermuth, *Heterocycles*, **1996**, *43*, 1459.

[142] L.-L. Gundersen, *Acta Chem. Scand.*, **1996**, *50*, 58.

[143] K. Edo, T. Sakamoto, and H. Yamanaka, *Chem. Pharm. Bull.*, **1979**, *27*, 193.

[144] A. Wada, J. Yamamoto, T. Hase, S. Nagai, and S. Kanatomo, *Synthesis*, **1986**, 555.

[145] K. Hirota, Y. Kitade, Y. Isobe, and Y. Maki, *Heterocycles*, **1987**, *26*, 355.

[146] T. Sakamoto, H. Arakida, K. Edo, and H. Yamanaka, *Heterocycles*, **1981**, *16*, 965.

[147] T. Sakamoto, H. Arakida, K. Edo, and H. Yamanaka, *Chem. Pharm. Bull.*, **1982**, *30*, 3647.

[148] M.-C. Viaud, P. Jamoneau, L. Savelon, and G. Guillaumet, *Tetrahedron Lett.*, **1996**, *37*, 2409.

[149] J. J. Chen, J. A. Walker, W. Liu, D. S. Wise, and L. B. Townsend, *Tetrahedron Lett.*, **1995**, *36*, 8363.

[150] K. S. Gudmundsson, J. C. Drach, and L. B. Townsend, *Tetrahedron Lett.*, **1996**, *37*, 6275.

[151] P. Melnyk, B. Legrand, J. Gasche, P. Ducrot, and C. Thal, *Tetrahedron*, **1995**, *51*, 1941.

[152] S. Y. Cho, S. S. Kim, K. H. Park, S. K. Kang, J. K. Choi, K. J. Hwang, and E. K. Yum, *Heterocycles*, **1996**, *43*, 1641.

[153] P. Blurton, A. Brickwood, and D. Dhanak, *Heterocycles*, **1997**, *45*, 2395.

[154] R. C. Larock, E. K. Yum, and M. D. Refvik, *J. Org. Chem.*, **1998**, *63*, 7652.

[155] F. Ujjainwalla and D. Warner, *Tetrahedron Lett.*, **1998**, *39*, 5355.

[156] S. S. Park, J.-K. Choi, E. K. Yum, and D. C. Ha, *Tetrahedron Lett.*, **1998**, *39*, 627.

[157] D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, S. Gronowitz, and L. A. Cohen, *Tetrahedron Lett.*, **1993**, *34*, 2823.

[158] E. Desarbre and J. Y. Merour, *Tetrahedron Lett.*, **1996**, *37*, 43.