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Cross-Coupling Reactions on Azoles with Two and More Heteroatoms

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Recent progress in the field of transition-metal-catalyzed cross-coupling reactions on various azole systems is summarized. Most important C–C- and C–X-bond formation methodologies (Negishi, Suzuki–Miyaura, Stille, Kumada–Corriu–Tamao, Hiyama, Sonogashira, Heck, C–H activation) are reviewed and discussed for the imidazole, oxazole, thiazole, pyrazole, isoxazole, and isothiazole system, as well as for azoles with more than two heteroatoms. This review covers the literature that appeared in the past ten years up to the end of 2005 with corresponding azoles used either as metal organyl or halide (including triflates and some other less frequently applied leaving groups); literature describing azole structures only as ligands was not included.

1. Introduction

Transition-metal-catalyzed cross-coupling reactions are a well established tool for C–C and C–X (X = O, N, S) bond formation.[1–3] Many publications focus on the development of new catalysts, whose efficiency is tested mainly in the formation of biaryl compounds, relative to existing methods.[4–11] Heterocyclic examples remain rare in these experiments and are typically found in readily available thiophene- or pyridine derivatives.[12–15] Complementing the preceding review by Banwell et al. on Pd-catalyzed reactions on pyrroles, this contribution covers metal-assisted cross-coupling reactions on azoles incorporating additional heteroatoms.[16]

Examples for cross-coupling reactions on azole derivatives are mainly limited to reactions leading to prominent target compounds with only very few methodological studies. The Negishi cross-coupling, for example, is a well-established method in the formation of 2,4-bithiazoles, an important structural motif in the series of cystothiazoles. In those areas, where such target compounds are lacking, cross-coupling chemistry was naturally less frequently considered. A second limiting factor in some cases is the availability of the desired azole coupling partners. For example, Suzuki–Miyaura cross-coupling reactions suffer from the fact that corresponding azoleboronic acids or esters are hardly available so far; sometimes even the required haloazole precursors are not easily accessible. Although these factors led to a limited number of cross-coupling examples in this heterocyclic series, interesting reactions and applications were introduced in recent years and may give rise to further improvement and broadening of the scope of this methodology within the area of azole chemistry. This review covers progress in azole cross-coupling chemistry including our own recent research in this field (successful preparation of a thiazoleboronic acid ester) with major focus on the recent ten years up to the end of 2005, as older work is covered by previous overviews.[17,18]

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2. Imidazoles

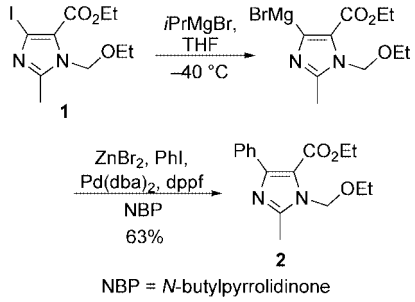
Within the azole series, imidazole is maybe the most prominent ring system and is encountered in many compounds with biological activity or in natural products. Therefore, the most cross-coupling literature is available, and many different methods have successfully been applied. Here some data is also available where different cross-coupling methodologies have been compared, providing interesting results for synthetic chemists.

2.1. Negishi Reaction

Several examples for Negishi cross-couplings were reported in imidazole chemistry. 5-Iodoimidazole **1** readily

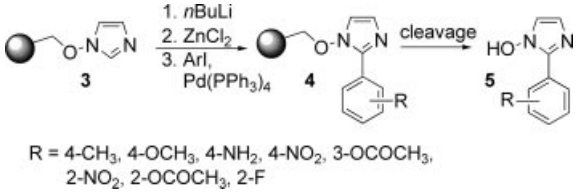
MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

underwent halogen–magnesium exchange. Transmetalation with $ZnBr_2$ and subsequent cross-coupling with iodobenzene gave product **2** in 63% overall yield (Scheme 1).[19]



Scheme 1.

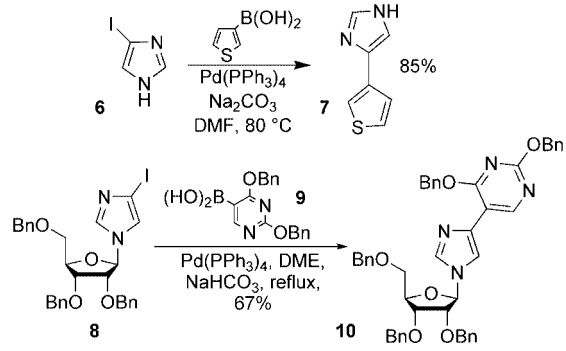
A Negishi reaction in the 2-position of imidazole was reported on the solid phase (Scheme 2). After introduction of $ZnCl_2$, cross-coupling with 4-iodotoluene was optimized. While Merrifield resin gave slightly higher yields for the cross-coupling reaction, Wang resin allowed much milder conditions for the subsequent cleavage. Successful C–C-bond formation was highly dependent on substituents on the applied halide (R = 2-NO_2, 2-$OCOCH_3$: no conversion; other examples with yields around 80%). In one case, 2-iodothiophene was successfully used as heterocyclic coupling partner yielding a hetaryl-hetaryl reaction product.[20]



Scheme 2.

2.2. Suzuki–Miyaura Reaction

Suzuki–Miyaura cross-coupling reactions have been reported on all three carbon positions. 3-Thiopheneboronic acid gave good yields in the hetaryl-hetaryl cross-coupling reaction with 4-iodoimidazole (**6**) without protection of the NH group (Scheme 3).[21] Highly functionalized 4-iodoimidazole **8** was cross-coupled with pyrimidineboronic acid **9** to give **10** in 67% yield (Scheme 3).[22] Other examples for the use of substituted 4-iodoimidazoles can be found in the literature.[23] Additionally, 5-iodoimidazoles were also successfully cross-coupled under Suzuki–Miyaura conditions, by using phenylboronic acids as coupling partners, in good yields (68–79%).[24]



Scheme 3.

In addition to iodides, bromides can serve as leaving groups. A double cross-coupling reaction in the 4-position

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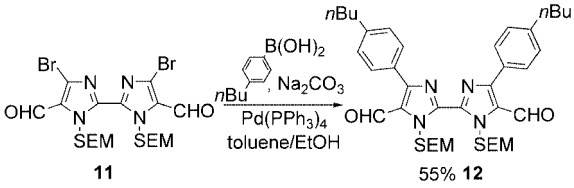
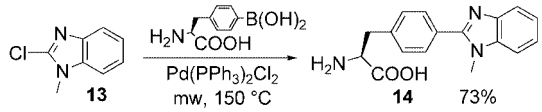
was accomplished on biimidazole **11** to give **12** in 55% yield (Scheme 4).[25]



Scheme 4.

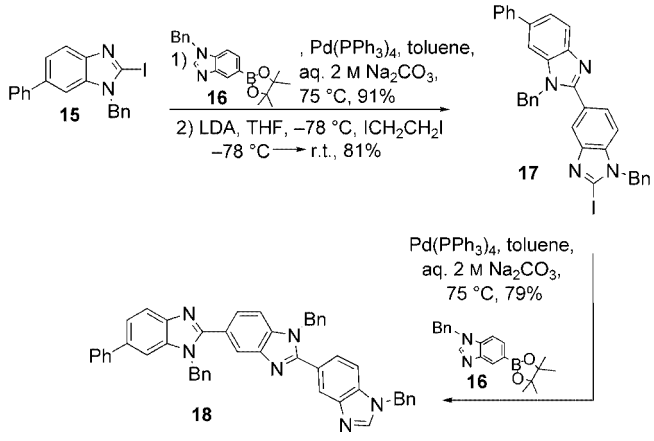
In a study on the preparation of 4-arylated phenylalanines, chlorine in the 2-position of **13** was found to be a suitable leaving group, and good yields were obtained for this transformation under microwave irradiation (Scheme 5).[26] A similar example using conventional heating (DME, reflux) was also reported and gave comparable yields (65%).[27]



Scheme 5.

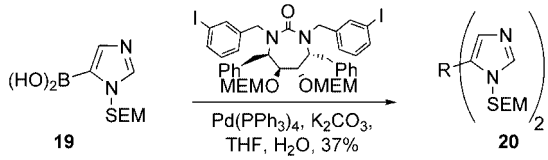
As expected, the reaction is generally applicable with iodine in the highly activated 2-position. A number of arylboronic acids were successfully cross-coupled; even sterically demanding boronic acids gave good yields (>70%) under optimized conditions. Only 3-nitrophenylboronic acid gave low yields of 15% independent of the reaction conditions applied.[28] Recently, bromine was investigated as a leaving group in the 2-position and enabled high yields (usually >90%) in the cross-coupling reaction with a number of phenylboronic acids.[29]

In the course of a synthetic route to terbenzimidazoles, which act as potent topoisomerase I poisons, two iterative couplings with pinacol boronate esters were carried out in the 2-position of the benzimidazole systems (Scheme 6). Both cross-coupling steps gave good yields under standard Suzuki–Miyaura conditions (91% and 79%).[30]



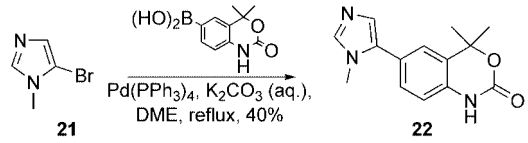
Scheme 6.

As for the majority of heterocyclic systems, the formation of boronic acids in the azole series is a difficult task and was not accomplished often. It seems that these compounds suffer from a limited stability due to rapid deboronation, especially under basic conditions required in Suzuki–Miyaura cross-coupling reactions. So far, 5-imidazoleboronic acid derivatives have been prepared (**19** in 95%), characterized, and successfully cross-coupled (Scheme 7).[31]



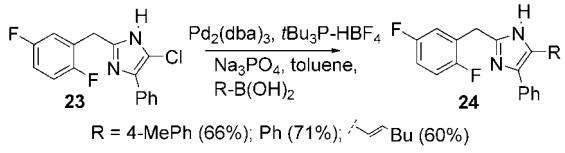
Scheme 7.

Suzuki–Miyaura cross-coupling was also reported in the 5-position. 5-Bromo-1-methyl-1*H*-imidazole (**21**) was cross-coupled with a heterocyclic boronic acid to **22** in 40% yield under standard reaction conditions (Scheme 8).[32]



Scheme 8.

Remarkably, chlorine in the 5-position can also be used as a leaving group in Suzuki–Miyaura cross-coupling reactions. Direct coupling of the unprotected imidazole **23** with various aryl/vinyl boronic acids was accomplished in good yields without optimization (Scheme 9).[33]

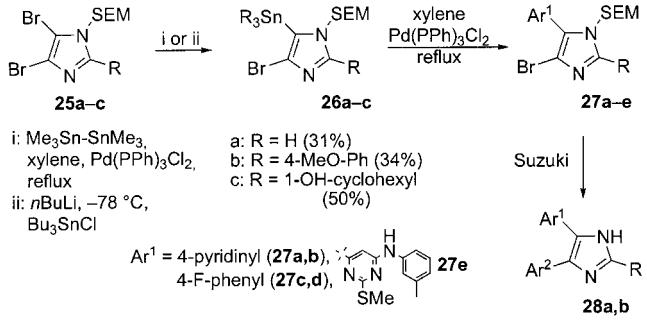


Scheme 9.

2.3. Stille Reaction

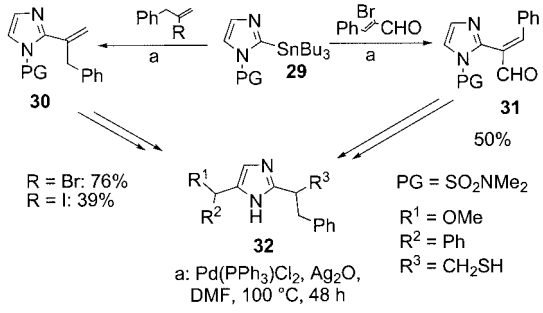
The Stille methodology is well established in the azole series, in general, and it is particularly important in imidazole chemistry. 4,5-Dibromoimidazoles **25a**–**c** were converted into the corresponding stannanes **26a**–**c** either by a Pd-assisted reaction with hexamethyldistannane or by bromine–lithium exchange and subsequent quenching with Bu_3SnCl (Scheme 10). The first method was only successful for R = H (**26a**: 31%). In the cases of R = 4-methoxyphenyl (**26b**: 34%) and R = 1-hydroxycyclohexyl (**26c**: 50%), the second method had to be applied. The subsequent Stille cross-coupling gave varying yields (24–74%). 4-Bromopyridine gave the best results (55%, R = 4-MeOPh; 74%, R = H). 4-Fluorobromobenzene gave considerably lower yields (36%, R = H; 24%, R = 4-MeOPh). Substituted bromopyrimidine gave 34% yield (R = 1-OH-cyclohexyl). In two ex-

amples, the remaining bromine in the 4-position was used for a Suzuki–Miyaura cross-coupling with 4-fluorophenylboronic acid to give the corresponding diarylated compounds **28a**,**b** in 65% and 68% yield, respectively (Scheme 10).[34]



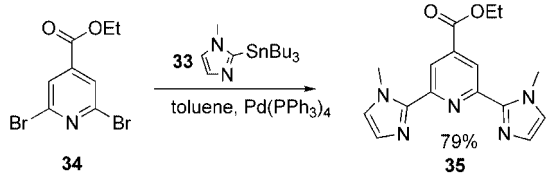
Scheme 10.

In the course of the preparation of a new inhibitor class of the metalloprotease Neprilysin, a Stille approach was envisaged. Cross-coupling of stannane **29** with halo-olefins gave the desired products in fairly good yields (Scheme 11). Stoichiometric amounts of Ag_2O seemed to accelerate the reaction. Interestingly, better yields were obtained when bromides were used instead of iodides, but no explanation for this finding was given.[35]



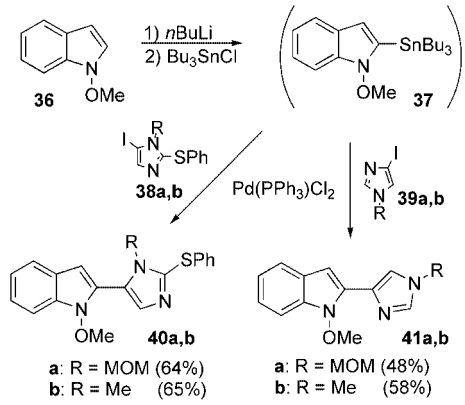
Scheme 11.

An efficient double Stille cross-coupling with 1-methyl-2-(tributylstannyl)-1*H*-imidazole (**33**) was reported. Upon reaction with coupling partner **34**, 79% of the 2,6-diimidazol-2-yl compound **35** was obtained (Scheme 12). This product represented a key intermediate in the synthesis of 4-functionalized terdentate pyridine-based ligands.[36] Imidazole **33** was also cross-coupled with 4-fluoroiodobenzene in 70% yield.[37]



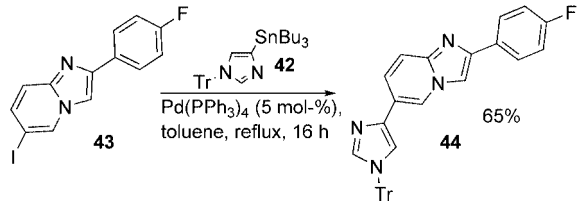
Scheme 12.

4-Iodoimidazoles **39a**,**b** were cross-coupled with (tributylstannyl)indole **37** in 48% (**41a**) and 58% (**41b**) yield.[38] 5-Iodoimidazoles **38a**,**b** gave slightly better yields (64% and 65% for **40a** and **40b**, respectively) in the same reaction (Scheme 13).[39]



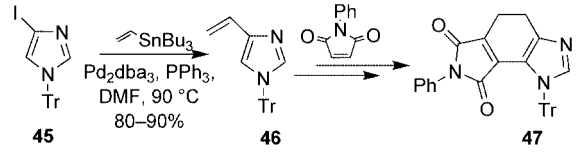
Scheme 13.

In the course of studies on the reactivity of 6-halo-imidazo[1,2-*a*]pyridine derivatives in Negishi- and Stille coupling reactions, N-protected 4-(tributylstannyl)imidazole **42** was converted with iodide **43** under $Pd(PPh_3)_4$ catalysis to **44** in 65% yield (Scheme 14).[40]



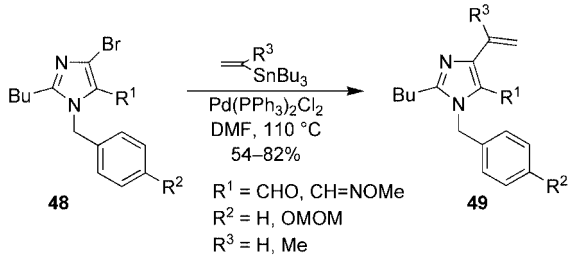
Scheme 14.

N-Protected 4-iodoimidazole **45** can effectively be cross-coupled with tributyl(vinyl)stannane (80–90%). The so-obtained **46** was used as substrate in Diels–Alder reactions with *N*-phenylmaleimide (Scheme 15) to finally afford **47**.[41]



Scheme 15.

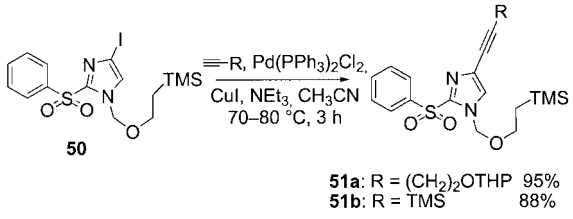
In another report, the reaction of alkenylstannanes with substituted 4-bromoimidazole **48** was investigated, and the corresponding products **49** were obtained in 54–82% yield (Scheme 16).[42]



Scheme 16.

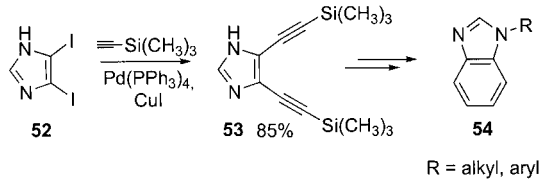
2.4. Sonogashira Reaction

Sonogashira reactions are nowadays well-established in imidazole chemistry. 4-Iodoimidazole **50** proved to be an excellent substrate for this cross-coupling reaction. Under $Pd(PPh_3)_2Cl_2$ catalysis and with addition of CuI, two terminal alkynes were converted to **51a** in 95% and **51b** in 88% yield (Scheme 17).[43] Other N-protected 4-iodoimidazoles were applied to the Sonogashira protocol with similar good results.[44,45]



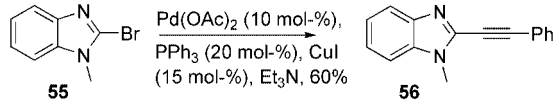
Scheme 17.

A double Sonogashira reaction was reported in a synthetic sequence towards benzimidazoles **54**. 4,5-Diiodoimidazole (**52**) was subjected to the classical Sonogashira conditions with TMS-acetylene and gave **53** in 85% yield (Scheme 18). It is noteworthy that the imidazole-NH did not require protection in this case.[46,47]



Scheme 18.

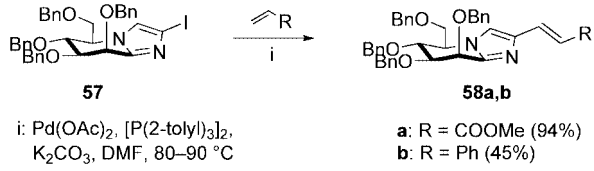
In the benzimidazole series, bromine was also reported as a versatile leaving group in the 2-position of benzimidazole **55** (Scheme 19) to give **56** in 60% yield.[48,49] Other examples in which iodide is the leaving group and $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ is the catalyst are reported in the literature.[50,51]



Scheme 19.

2.5. Heck Reaction

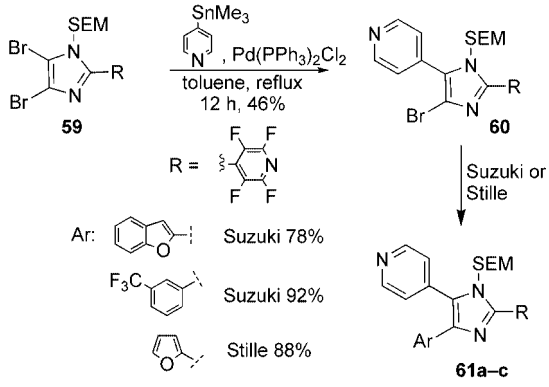
Only few examples of Heck reactions on imidazoles are reported in the recent literature. Heck cross-coupling in the 5-position of the imidazole was applied in the course of the synthesis of *manno*-configured tetrahydroimidazopyridines. Standard Heck conditions [$Pd(OAc)_2$, PPh_3, Et_3N or K_2CO_3, DMF] gave lower yields (54% and 25%) but using Herrmann's catalyst[52] instead, significantly improved the yield (94% and 45%, Scheme 20).[53]



Scheme 20.

2.6. Comparative Examples

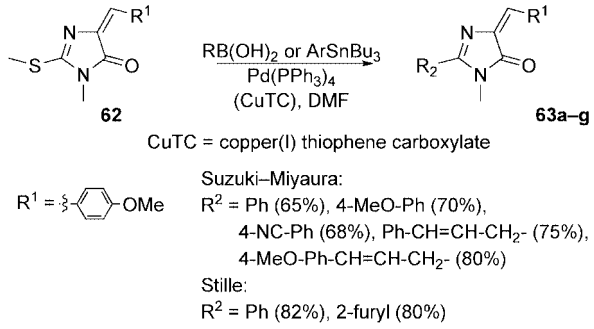
In some cases, different cross-coupling methods were applied on specific imidazole systems, which enabled comparison of various methods. For example, 4,5-dibromoimidazole **59** was used in sequential cross-coupling reactions. Initially, a 4-pyridinyl substituent was introduced in the 5-position in 46% yield for compound **60** by a Stille reaction with 4-(trimethylstannyl)pyridine. The remaining leaving group in the 4-position of **60** was subsequently used for a second arylation to **61a–c** either by a Suzuki–Miyaura or by another Stille reaction; these two methods proved to be equally successful (Scheme 21).[54] Another comparison between Suzuki–Miyaura and Stille reactions can be found in the literature.[55]



Scheme 21.

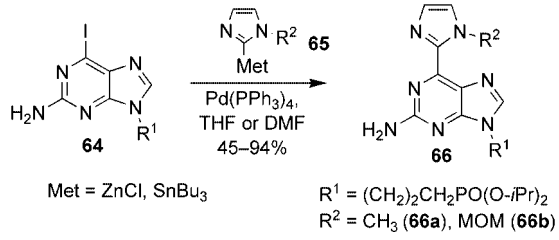
In one case, SMe was reported to be an efficient leaving group in the 2-position of imidazole derivative **62** in both

Suzuki–Miyaura and Stille cross-coupling reactions. Individually optimized reaction conditions for each arylboronic acid gave 65–80% yield (**63a–e**) within 15 min reaction time. 4-Substituted phenyl- or vinylboronic acids were applied to the reaction. The addition of copper was essential in the Suzuki–Miyaura examples. The Stille reaction using $ArSnBu_3$ (Ar = Ph, 2-furyl) gave similarly good results (82% **63f** and 80% **63g**) (Scheme 22).[56]



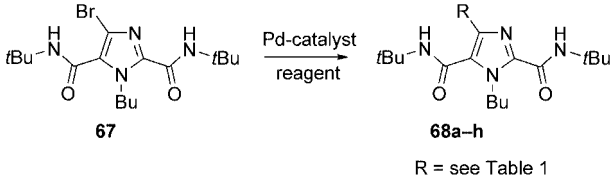
Scheme 22.

6-Iodopurine **64** was cross-coupled with methyl- or MOM-protected 2-metalimidazoles **65**. Using either zinc or tin organyls with the Negishi reaction gave better yields of **66** (**66a**: 94%; **66b**: 76%). The corresponding Stille reaction gave lower yields of 61% for **66a** and 45% for **66b** (Scheme 23).[57,58]



Scheme 23.

Bromoimidazole **67** was subjected to Heck, Sonogashira, Suzuki–Miyaura, and Stille cross-coupling (Scheme 24). Two examples were reported for each coupling reaction, and in every case the desired compound was obtained. Yields varied from moderate 37% in the Sonogashira reaction with 1-hexyne to excellent 85% in the Heck reaction with methyl acrylate (Table 1).[59]



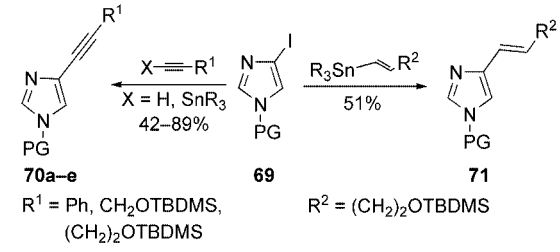
Scheme 24.

Whenever Heck or Sonogashira cross-couplings are not effective, the Stille methodology may sometimes give better results. Alkenyl- and alkynylstannanes are often more easily accessible and can be efficiently cross-coupled. For example, N-protected 4-iodoimidazole **69** was subjected to the Sonogashira reaction with several alkynes to give **70a–e** (42–89%). Alternatively, the corresponding Stille reactions were investigated and gave comparable results (47–85%) (Scheme 25).[60,61] The cross-coupling of alkenylstannanes was in that course favored over the Heck reaction (51% for **71**). The latter method failed to give the desired cross-coupling products, and only homo-coupling to 4,4′-biimidazoles was observed.[62]

Table 1. Various cross-coupling reactions of **67**.

Entry	Reagent	Conditions[a]	R[b]	Yield [%]
1	MeOOC	A	MeOOC	85
2	MeO	A	MeO	43
3	$SnBu_3$	B		65
4	O $SnBu_3$	B	O	76
5	$B(OH)_2$ OHC	C	OHC	63
6	OHC $B(OH)_2$	C	OHC	73
7	N	D	N	46
8		D		37

[a] A: $Pd(OAc)_2$, PPh_3, NEt_3, DMF, 60 °C, 1.5 h; B: $Pd(PPh_3)_4$, NEt_3, DMF, 60 °C, 6 h; C: $Pd(PPh_3)_4$, aq. Na_2CO_3, toluene, EtOH, 80 °C, 6 h; D: $Pd(PPh_3)_4$, NEt_3, 60 °C, 6 h. [b] Refers to product **68**, see Scheme 24.



Scheme 25.

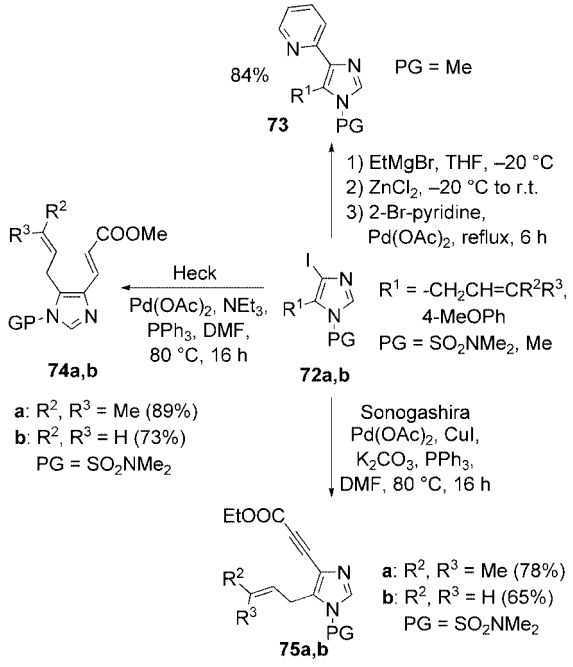
In another study, Negishi, Sonogashira, Heck, and Suzuki–Miyaura reactions on iodoimidazole derivatives **72** were reported, and good yields were obtained in all cases (Negishi: 84% **73**; Sonogashira: 65% **75b** and 78% **75a**; Heck: 73% **74b** and 89% **74a**) (Scheme 26).[63]

Diiodoimidazoles **76a–c** (**a**: PG = Bn, **b**: PG = SO_2NMe_2, **c**: PG = Me; R = I) were used in a principal study to establish the coupling ability of both iodides in Suzuki–Miyaura reactions. Both iodides could be cross-coupled in high yields (91% and 95%, Table 2, entries 2

Table 2. Cross-coupling of iodides **76a**–**f** with various arylboronic acids.

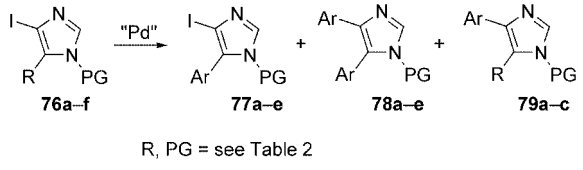
Entry	R[a]	PG[a]	Ar–B(OH)$_2$	Method[b]	coupling at 5	coupling at 4 and 5	coupling at 4
1	I	Bn	4-F-Ph[c]	A	27	53	–
2	I	Bn	4-F-Ph[d]	A	–	91	–
3	I	Bn	3,4-(MeO)$_2$-Ph[d]	B	–	95	–
4	I	SO_2NMe_2	Ph[c]	C	16	24	–
5	I	Me	Ph[c]	B	24	48	–
6	4-MeO	Me	4-F-Ph[c]	B	–	–	79
7	isoprenyl	Me	4-Pyridyl[c]	B	–	–	65
8	4-MeS	Bn	3-MeO-Ph[c]	B	–	–	77

[a] See Scheme 27. [b] A: Na_2CO_3, EtOH, H_2O, DME, $Pd(PPh_3)_4$, 95 °C; B: CsF, DMF, $Pd(OAc)_2$, dioxane, ligand, 80 °C; C: K_2CO_3, DMF, $Pd(PPh_3)_4$, 60 °C. [c] 2 equiv. [d] 4 equiv.



Scheme 26.

and 3) when 4 equiv. of boronic acids were applied. In the presence of only 2 equiv. of coupling partner, mixtures of 5-monoarylated (**77a**–**e**) and 4,5-diarylated (**78a**–**e**) compounds were obtained (entries 1, 4, 5). The 4-iodoimidazoles **76d**–**f** (**d**: R = 4-MeO, **e**: R = isoprenyl, **f**: R = 4-MeS), already bearing substituents in the 5-position, were also successfully cross-coupled in good yields (65–79%, entries 6–8) to the 4,5-disubstituted compounds **79a**–**c** (Scheme 27).[63]

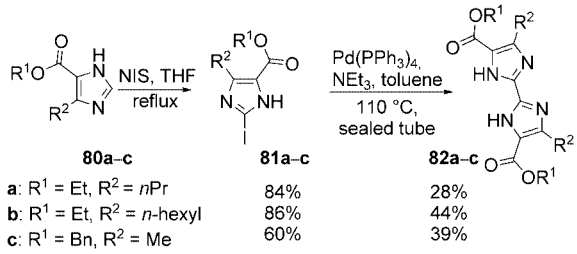


Scheme 27.

2.7. Other Methods

2.7.1. Homo-Coupling

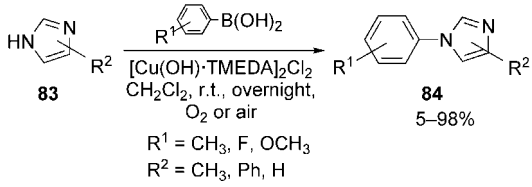
The homo-coupling of 2-iodoimidazoles **81a**–**c** was reported under $Pd(PPh_3)_4$ catalysis. Applying sealed tube conditions, the corresponding biimidazoles **82a**–**c** were obtained in 28–44% yield (Scheme 28). Although the yields were low, other investigated cross-coupling methods (e.g. Ullmann-type) proved to be inferior.[64,65]



Scheme 28.

2.7.2. C–N Bond Formation

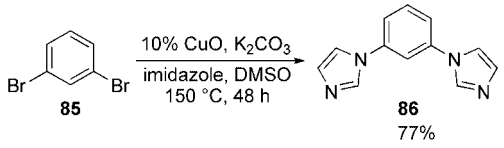
A variety of *N*-arylimidazoles were prepared by cross-coupling of arylboronic acids with imidazoles **83** in the presence of $[Cu(OH)TMEDA]_2Cl_2$. The corresponding 1-arylated imidazoles **84** were obtained in usually good yields, typically between 60% and 90% (2-methoxybenzeneboronic acid gave an exceptionally low yield of 5%, Scheme 29). Aerobic conditions were required to ensure conversion to the desired products, as O_2 plays a crucial role in regenerating the active catalyst within the catalytic cycle.[66,67] Similar methods were also reported with other copper salts.[68–71]



Scheme 29.

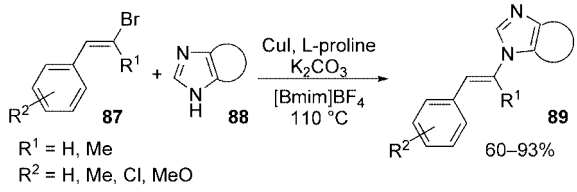
In the course of the development of new bis(carbene) ligands for cross-coupling reactions, double copper-catalyzed C–N bond formation on 1,3-dibromobenzene (**85**) provided 1,1′-(1,3-phenylene)-bis(1*H*-imidazole) (**86**) in 77% yield (Scheme 30). By heating this compound with alkyl halides, the corresponding imidazolium salts were obtained and were tested as ligands in Suzuki–Miyaura cross-coupling reactions.[72] Recently, sterically demanding aryl

iodides were applied in C–N bond formations with imidazole under mild reaction conditions.[73] Buchwald et al. also describe the copper–diamine-complex-catalyzed N-arylation of imidazoles and some other π-excessive nitrogen heterocycles (pyrroles, pyrazoles, indazoles, triazoles).[74]



Scheme 30.

Ullmann-type C–N bond formation of vinyl bromides **87** and imidazole derivatives **88** in ionic liquids was also reported. L-Proline was used as ligand, and usually high yields of **89** were obtained (60–93%). The double-bond geometry of the vinyl bromides was retained (Scheme 31). The metal catalysts immobilized in the reaction medium could be reused, and up to four cycles were performed without a significant drop of yield.[75] Apart from ionic liquids, other solvents were reported to enable efficient transformations (DMSO, DMF, *i*PrOH, DMA).[76,77]

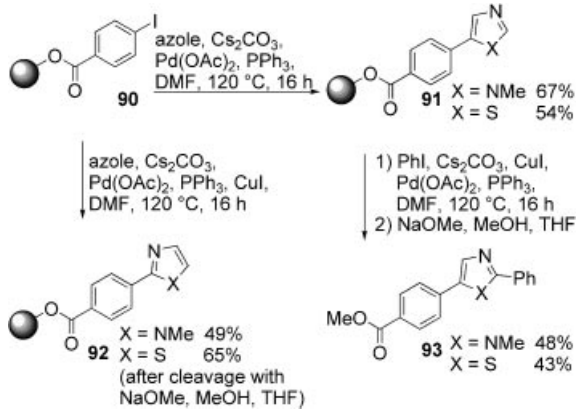


Scheme 31.

2.7.3. Direct Arylations

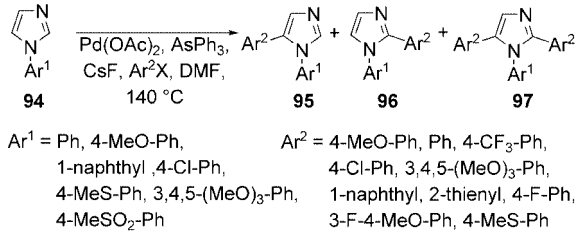
Direct arylation of imidazole and thiazole on a solid support by utilizing CuI as additive was reported; this proved to have a dramatic effect on the selectivity of the reaction. In the absence of CuI, the arylation was directed exclusively to the 5-position of the azole system (**91**: 67% for *N*-methylimidazole, 54% for thiazole). With addition of CuI, the selectivity changed, and direct arylation occurred in the 2-position, as is the case in solution-phase chemistry (**92**: 49% for *N*-methylimidazole, 65% for thiazole). Products with aryl substituents in the 5-position were subjected to an additional C–C-bond-formation step and subsequently arylated in the 2-position to give unsymmetrically diarylated compounds **93** (Scheme 32).[78]

A detailed study of the direct arylation of 1-aryl-1*H*-imidazoles[79] was reported in the literature: Initially starting from commercially available 1-phenyl-1*H*-imidazole, the reaction conditions for arylation in the 5-position were optimized with respect to parameters like catalyst, ligand, base, solvent, temperature, and time, as well as the ratio of the applied substrates, before a number of substituted 1-aryl-1*H*-imidazoles **94** were prepared to investigate the scope of the reaction. The 5-arylation to **95** was performed



Scheme 32.

by using the optimized reaction conditions [$Pd(OAc)_2$, $AsPh_3$, CsF, DMF, 140 °C] (Scheme 33). Interestingly, it was found that the halide in Ar^2X had no clear influence on the outcome of the reaction, as both iodine and bromine gave superior results in various examples (Table 3, entries 1–6, 8, 9). The influence of the substituents on Ar^1 had a significant influence on the outcome of the reaction. The arylation was most efficient when electron-rich aryl groups were linked to N-1 (entries 8–10) and failed when an electron-withdrawing substituent (4-$MeSO_2$) was attached (entries 12–13). In most successful examples, good to complete selectivity to the 1,5-diarylated compounds **95** was achieved



Scheme 33.

Table 3. Direct arylation of 1-aryl-1*H*-imidazoles **94**.[a]

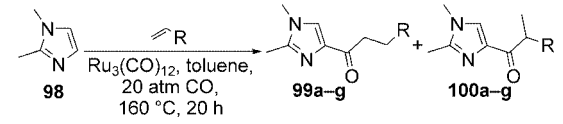
Entry	Ar^1	Ar^2	X	Ratio 1,5/1,2/1,2,5	Yield [%]
1	Ph	4-MeO-Ph	I	95:5:0	49
2	Ph	4-MeO-Ph	Br	100:0:0	43
3	Ph	4-CF_3-Ph	I	86:5:9	38
4	Ph	4-CF_3-Ph	Br	76:0:24	59
5	4-MeOPh	4-MeO-Ph	I	88:3:9	36
6	4-MeOPh	4-MeO-Ph	Br	52:11:37	22
7	4-MeOPh	3,4,5-$(MeO)_3$-Ph	I	–	–
8	3,4,5-$(MeO)_3$Ph	4-MeO-Ph	I	87:2:11	40
9	3,4,5-$(MeO)_3$Ph	4-MeO-Ph	Br	100:0:0	61
10	3,4,5-$(MeO)_3$Ph	3-F,4-MeO-Ph	Br	95:0:5	72
11	4-MeSPh	4-F-Ph	I	17:43:40	9
12	4-$MeSO_2$Ph	4-MeO-Ph	I	–	–
13	4-$MeSO_2$Ph	4-MeO-Ph	Br	–	–

[a] See Scheme 33.

(76–100%) and only minor amounts of 1,2-diarylated **96** (0–5%) and 1,2,5-triarylated **97** (0–24%) were isolated. When 4-fluoroiodobenzene was used as halide, the selectivity changed, and the 1,2-diarylated compound was predominantly formed (entry 11). Selected examples are compiled in Table 3. It has to be mentioned that extremely long reaction times were required (17–240 hours), and in most cases only moderate yields (9–72%) were reported.[80] Just recently, improved results have been reported upon addition of CuI.[81]

2.7.4. Carbonylation Reactions

The reaction of 1,2-dimethylimidazole (**98**) with alkenes under 20 atm CO in toluene gave the corresponding carbonyl compounds in 42–88% yield (Scheme 34). Usually, the linear isomer **99** was strongly favored. In one case, a cyclic alkene (cyclohexene) was applied and gave 50% of the desired carbonyl compound. Among a variety of transition-metal complexes investigated in course of the study, $Ru_3(CO)_{12}$ turned out to be most efficient for this transformation.[82]



a: R = Bu	68% (94:6)	**e**: R = $SiMe_3$	66% (>99:1)
b: R = Ph	74% (75:25)	**f**: R = CH_2SiMe_3	61% (94:6)
c: R = 2-MeC_6H_4	77% (93:7)	**g**: R = CH_2CN	42% (87:13)
d: R = *t*Bu	88% (>99:1)		

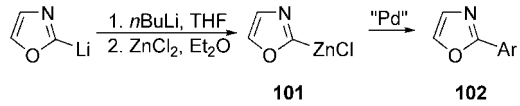
Scheme 34.

3. Oxazole

The oxazole motif is encountered in a number of compounds with interesting biological activity, either natural products or rationally designed drugs. Additionally, several interesting materials containing oxazole rings were reported recently.[83,84] As these scaffolds usually contain highly substituted oxazoles, transition-metal-catalyzed cross-coupling reactions should offer efficient methodologies for a diversity-oriented synthetic strategy.

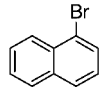
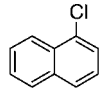
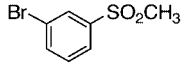
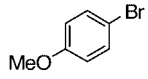
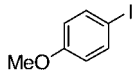
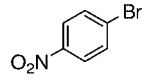
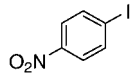
3.1. Negishi Reaction

Negishi cross-coupling reactions on oxazoles were reported very early, but showed rather limited applicability. From the three possible positions for the formation of organozinc reagents, only the 2-oxazolylzinc species **101** was successfully prepared and subsequently cross-coupled with aryl iodides and triflates to compounds **102**.[85,86] Aryl bromides gave considerably lower yields after long reaction times. Recently, the use of solid $ZnCl_2$ rather than a solution (commercially available in Et_2O) in organometal formation allowed cross-coupling of aryl bromides to proceed in good yields (Scheme 35); however, long reaction times (typically 24 hours) were still necessary. Two heterocyclic halides (2-bromofuran and 2-bromopyridine) were also successfully cross-coupled.[87] Selected examples are presented in Table 4.



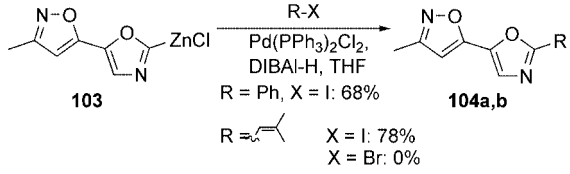
Scheme 35.

Table 4. Negishi cross-coupling of **101** with aryl- and heteroaryl halides.[a]

Entry	Halide	Time [h]	Yield [%]
1		24	73
2		24	–
3		0.5	90
4		24	19
5		24	>80[b]
6		24	82
7		0.5	98
8		24	60
9		1	77

[a] See Scheme 35. [b] According to HPLC.

In the course of deuteriation studies on oxazoles aimed to elucidate the actual equilibrium of 2-metalated oxazole species with its ring-opened form, Negishi cross-couplings were also reported. The most outstanding example was that of isoxazolyloxazole **103** with iodobenzene or 1-halo-2-

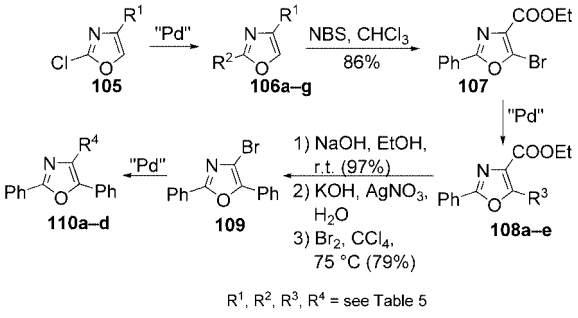


Scheme 36.

methylprop-1-ene. The two investigated iodides gave reasonable yields of the cross-coupling products **104a**,**b** but reaction with the bromoalkene failed (Scheme 36).[88]

3.2. Suzuki–Miyaura Reaction

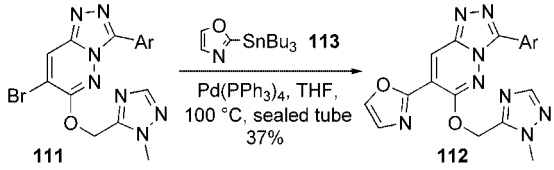
Suzuki–Miyaura reactions on oxazole are rare. So far, no oxazoleboronic acids have been reported and therefore oxazole is only used as the organic electrophile. For 5-bromo-2-phenyloxazole, fairly good yields have been reported.[89] The Stille reaction proved to be comparable,[90] as was the case when chlorine was used as leaving group in the 2-position.[91] In an example, the chlorine in the 2-position of **105** was cross-coupled to **106a**–**g** under Suzuki–Miyaura, Stille, Negishi, and Sonogashira reaction conditions. The so-obtained 2-phenyloxazole-4-carboxylic acid ester **106d** was brominated in the 5-position to **107** to enable a second cross-coupling step. Again Suzuki–Miyaura, Stille, Negishi, and Sonogashira examples were reported (**108a**–**e**). The obtained 2,5-diphenyloxazole-4-carboxylic acid ester **108a** was converted into the 4-bromo derivative **109** and again subjected to the four cross-coupling methods mentioned above (Scheme 37).[92] The results of selected examples are reported in Table 5.



Scheme 37.

3.3. Stille Reaction

The Stille method is also the most frequently used cross-coupling reaction in oxazole chemistry. Oxazole derivatives are used either as the halides or the organometal species in Stille cross-couplings. Readily available 2-(tributylstannyl)-oxazole (**113**) was successfully applied in a number of reactions, even on complex substrates. In an effort to synthesize trisubstituted triazolo[4,3-*b*]pyridazines, a compound class identified as subtype selective ligands for the benzodiazepine binding site of GABA-A receptors, 2-(tributylstannyl)-oxazole was cross-coupled with bromide **111** to give the cross-coupling product **112** in not optimized 37% yield (Scheme 38). The cross-coupling was carried out in a sealed tube in THF at 100 °C.[93]



Scheme 38.

Stannane **113** was also used in the synthesis of a series of highly substituted 2-pyridones from triflate precursors. The reaction was carried out in DMF at 100 °C in 44% yield. Additionally, imidazole-2-zinc chloride (51%) and pyrazole-5-zinc chloride derivatives (28%) were used as organometallic compounds.[94]

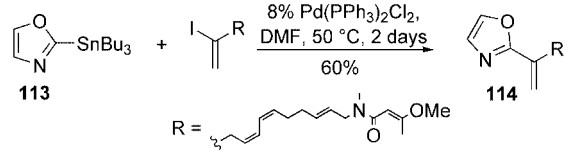
An alkenyliodide was also reported as coupling partner for 2-(tributylstannyl)oxazole **113**.[95] During efforts to synthesize ajudazol A, a pharmacologically active metabolite isolated from *Chondromyces crocatus*, Stille cross-coupling was performed in 60% yield to compound **114** (Scheme 39). It has to be noted that only the iodide was converted successfully in contrast to the corresponding bromide. Still, relatively high catalyst amounts (8%) and long reaction times

Table 5. Cross-coupling sequence of **105** to **110a**–**d**.

Entry	C2-subst.[a]	C4-subst.[a]	C5-subst.[a]	Method	Prod.[a]	Yield [%]
1	Ph (R^2)	benzyl (R^1)	–	Suzuki	**106a**	97
2	Ph (R^2)	benzyl (R^1)	–	Stille	**106a**	96
3	3-thienyl (R^2)	benzyl (R^1)	–	Suzuki	**106b**	60
4	vinyl (R^2)	benzyl (R^1)	–	Stille	**106c**	94
5	Ph (R^2)	COOEt (R^1)	–	Suzuki	**106d**	87
6	vinyl (R^2)	COOEt (R^1)	–	Stille	**106e**	84
7	2-pyridyl (R^2)	COOEt (R^1)	–	Negishi	**106f**	73
8	C≡CPh (R^2)	COOEt (R^1)	–	Sonogashira	**106g**	0
9	Ph	COOEt	Ph (R^3)	Suzuki	**108a**	93
10	Ph	COOEt	3,4-$(MeO)_2$Ph (R^3)	Suzuki	**108b**	91
11	Ph	COOEt	vinyl (R^3)	Stille	**108c**	82
12	Ph	COOEt	2-pyridyl (R^3)	Negishi	**108d**	76
13	Ph	COOEt	C≡CPh (R^3)	Sonogashira	**108e**	77
14	Ph	Ph (R^4)	Ph	Suzuki	**110a**	89
15	Ph	vinyl (R^4)	Ph	Stille	**110b**	83
16	Ph	2-pyridyl (R^4)	Ph	Negishi	**110c**	72
17	Ph	C≡CPh (R^4)	Ph	Sonogashira	**110d**	79

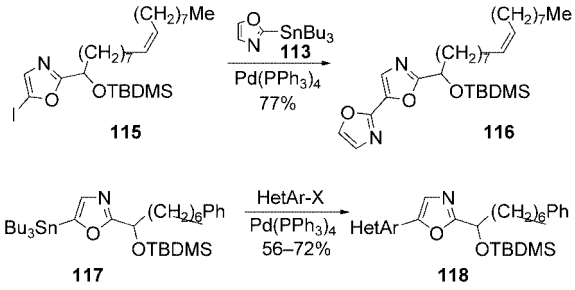
[a] See Scheme 37.

(2 days, DMF, 50 °C) were required, as the limited stability of the diene system did not permit higher reaction temperatures.



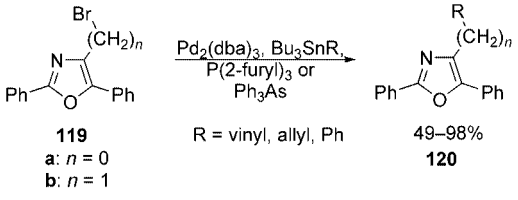
Scheme 39.

In another example, oxazole was used both as stannane and halide.[96] 5-Iodooxazole **115** was cross-coupled with **113** to give 77% of the corresponding bioxazole **116**. 5-Iodooxazole **115** was also cross-coupled with a number of other heterocyclic tributylstannyl-reagents (3-pyridazinyl, 2-pyrazinyl, 2- and 4-pyrimidinyl, 2-thienyl, 2-furyl, and 2-thiazolyl) in 43–77% yield. 5-(Tributylstannyl)oxazole **117** was also prepared by lithiation with *t*BuLi in the 5-position and subsequent quenching with Bu_3SnCl and cross-coupled with 2-iodopyrazine and 5-bromopyrimidine in acceptable yields (56 and 72%) (Scheme 40).



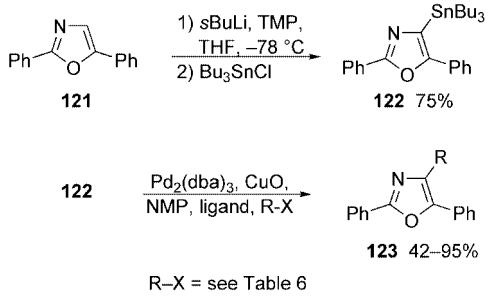
Scheme 40.

In an effort to prepare starting materials for comparative polymerization studies, 4-bromo-2,5-diphenyloxazole (**119a**) and 4-bromomethyl-2,5-diphenyloxazole (**119b**) were treated with various stannanes (Scheme 41). In most cases, very good yields of **120** were obtained (84–98%), with the reaction of **119a** with allyl(tributyltin) as a notable exception (49%).[97]



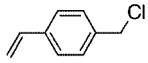
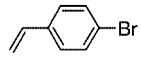
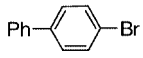
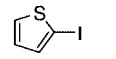
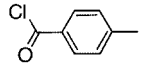
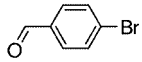
Scheme 41.

Since styrene-substituted oxazoles could not be prepared from bromooxazoles **119a**,**b**, 2,5-diphenyl-4-(tributylstannyl)oxazole (**122**) was synthesized from **121** by lithiation with *s*BuLi and subsequent quenching with Bu_3SnCl and reacted with a number of electrophiles including benzyl chlorides, aryl halides, and an acid chloride (Scheme 42, compounds **123**, Table 6).[97]



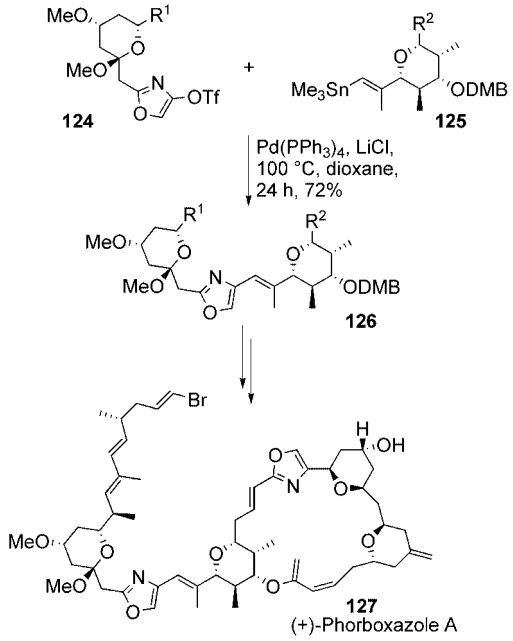
Scheme 42.

Table 6. Stille cross-coupling of **122**.

Entry	R–X[a]	Ligand, Temp.	Yield [%]
1		$AsPh_3$, 65 °C	95
2		(2-furyl)$_3$P, 65 °C	58
3		(2-furyl)$_3$P, 65 °C	51
4		(2-furyl)$_3$P, 80 °C	42
5		$AsPh_3$, 65 °C	69
6		(2-furyl)$_3$P, 65 °C	82

[a] See Scheme 42.

A very complex example was reported in the total synthesis of (+)-phorboxazole **127**. The oxazole triflate **124** was cross-coupled with the alkenylstannane **125** to give the desired product in 72% yield.[98] The best conditions for this

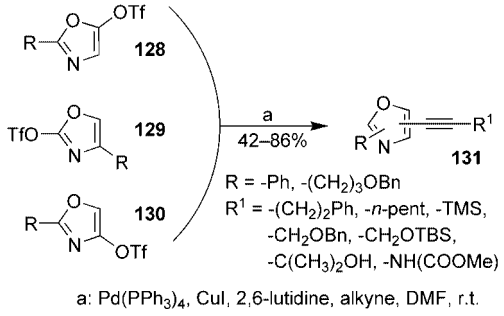


Scheme 43.

transformation were reported to be using $Pd(PPh_3)_4$ as catalyst upon addition of LiCl in dioxane in a sealed tube (Scheme 43).

3.4. Sonogashira Reaction

Sonogashira cross-coupling reactions on oxazoles are rare. Oxazole triflates **128**–**130** were systematically investigated, and the reaction conditions were optimized. $Pd(PPh_3)_4$ in combination with catalytic amounts of CuI were found to give quantitative conversion (isolated yields: 42–86%) to the cross-coupling products of the general structure **131** in the presence of NEt_3 as base, completely avoiding alkyne homo-coupling byproducts. These reaction conditions proved to be suitable only for 4- (**130**) and 5-oxazole triflates (**128**). The corresponding 2-oxazole triflates **129** were only hydrolyzed to 2-oxazolones. When 2,6-lutidine was applied for the reaction in the 2-position instead of NEt_3, the cross-coupling reaction was achieved already at room temperature (54–83%). The compatibility with the alkyne functionality was also investigated; a wide variety of functional groups was tolerated (alcohols, silanes, carbamates) (Scheme 44).[99] Similar research was reported for thiazole substrates; this is discussed later (Section 4.4.).



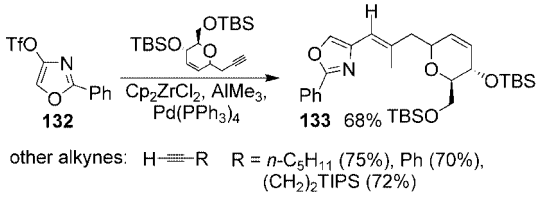
Scheme 44.

The method was successfully applied to the synthesis of the oxazole-containing side chain of leucascandrolide A, a double O-bridged, 18-membered macrolide isolated from the calcareous sponge *Leucascandra caveolata*.[100]

3.5. Other Methods

3.5.1. Carboalumination

In the course of studies towards the construction of the C26–C31-subunit of phorboxazole A, the use of 2-phenyloxazole-4-triflate (**132**) in a zirconium-catalyzed carboalumination reaction was reported. Carboalumination of an alkyne followed by Pd-catalyzed coupling with the triflate gave the alkenyloxazole **133** with the desired *E*-stereochemistry (Scheme 45). A number of alkynes were subjected to the reaction and gave good yields; however, the target subunit of phorboxazole A could not be successfully prepared. Alternatively, a Stille method was investigated, which finally afforded the desired compound.[101]

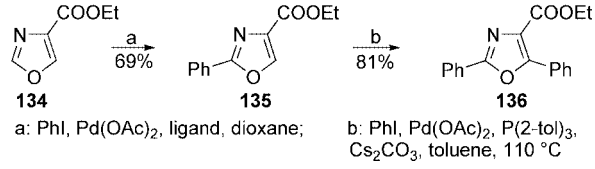


Scheme 45.

3.5.2. C–H Activation

A relatively new method in metal-catalyzed reactions is direct arylation by C–H activation. A method for the direct arylation of various heterocyclic systems including oxazole was developed. Depending on the reaction conditions, the parent oxazole can be arylated selectively in the 2- or 5-position; higher yields are obtained for the 2-position. The arylation in the 5-position was sometimes achieved in good yield when the 2-position was already bearing another aryl group.[102]

A similar study was reported recently. In this case, the oxazole was bearing a carboxylic acid ester in the 4-position (**134**). Optimized reaction conditions for arylation of the 2-position turned out to be $Pd(OAc)_2$ and IMes [*N*,*N*′-bis(mesityl)imidazol-2-ylidene] as the ligand. In that way, 88% of the desired regioisomer **135** was obtained accompanied by 11% of the 2,5-diarylated product **136**. Compound **135** was obtained in 46% yield in the absence of a ligand without any byproducts. Buchwald′s ligand [2-(dicyclohexylphosphanyl)biphenyl] improved this result to 69% also without byproducts. The second arylation in the 5-position needed $P(2\text{-tol})_3$ as ligand and Cs_2CO_3 as base. By this method, an overall yield of 81% of the desired product was obtained (Scheme 46).[103]



Scheme 46.

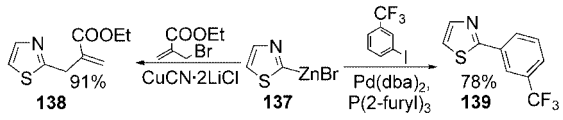
4. Thiazole

Just as oxazole, thiazole is found in a number of compounds with interesting properties, most prominent biological activities, and attractive qualities in material sciences. For example, vitamin B1 contains a thiazolium ring. Cross-coupling methods are becoming more and more competitive with classical cyclization reactions in developing complex thiazole-containing compounds.

4.1. Negishi Reaction

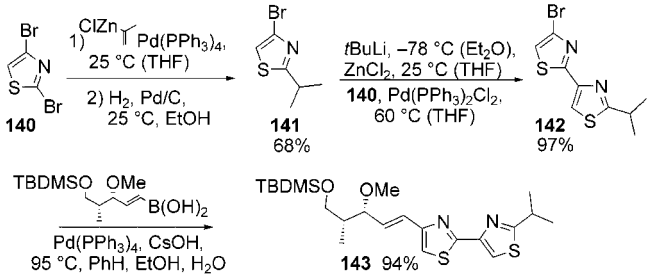
The Negishi reaction was utilized in thiazole chemistry both with thiazolylzinc halides and halothiazoles. Initially, thiazolylzinc halides were formed in the 2-position. The or-

ganozinc halide can be prepared from 2-bromothiazole and zinc dust; however, it is not necessary to use highly activated (Riecke) zinc. The obtained zinc organyl **137** was cross-coupled with aromatic or aliphatic electrophiles to give the corresponding products in 78% and 91% yield for **139** and **138**, respectively. In the latter case, copper was applied as catalyst instead of palladium (Scheme 47).[104] 2,4-Dibromothiazole has been used as halide in Negishi reactions; the cross-coupling took place selectively in the 2-position in 50–62% yield.[105]



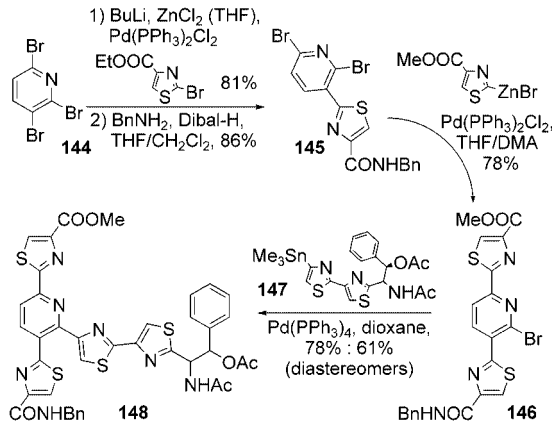
Scheme 47.

In the course of developing a total synthesis for cystothiazole E, an efficient Negishi cross-coupling strategy using 4-thiazolylzinc halide derivatives was established.[106] In a seminal strategy, three cross-coupling reactions were performed on the thiazole system. Initially, the isopropyl side chain was introduced by Negishi cross-coupling of 2,4-dibromothiazole (**140**) with isopropenylzinc chloride and subsequent hydrogenation. Then, the remaining bromide in the 4-position of **141** was transformed into the corresponding organozinc compound by use of *t*BuLi and $ZnCl_2$. Cross-coupling with **140** under $Pd(PPh_3)_2Cl_2$ catalysis gave the desired bithiazole **142** in 97% yield. Finally, the side chain was introduced in a Suzuki–Miyaura reaction with a suitable alkenylboronic acid ester (Scheme 48). The method was then extended and applied to the synthesis of cystothiazole A and C.[107] Later, the scope of the cross-coupling in the 4-position was also investigated.[108] While the Negishi reaction gave high yields (88–97%) as long as the substituent in the 2-position was an alkyl group, the reaction failed with alkynyl- or aryl substituents. Alternatively, a Stille reaction was successful in these cases (38–51%).



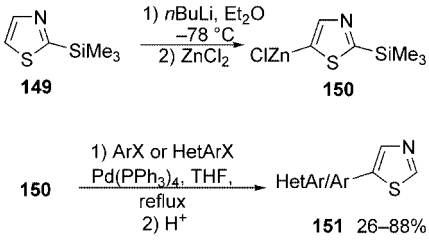
Scheme 48.

The Negishi reaction was also applied in a synthetic strategy towards the heterocyclic core of GE 2270 antibiotics. Three cross-coupling reactions with thiazole building blocks were performed. In the first reaction, a zinc organyl in the 3-position derived from 2,3,6-tribromopyridine (**144**) was cross-coupled with ethyl 2-bromothiazole-4-carboxylate in 81% yield. The intermediate was subsequently transferred into amide **145**, which was used as the halide in another Negishi cross-coupling. Reductive metalation of methyl 2-bromothiazole-4-carboxylate with zinc gave the cross-coupling partner, and the second thiazole ring was attached in 78% yield. Finally, **146** was cross-coupled with bithiazolyl stannane **147** in 61–78% yield to give the desired compound **148** (Scheme 49).[109]



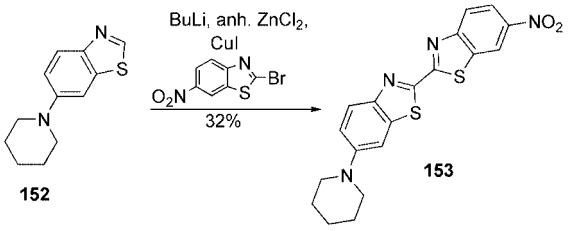
Scheme 49.

The formation of zinc organyls in the 5-position of thiazole was also successful, and cross-coupling reactions were performed. In one example, the 2-position was blocked with TMS before the organozinc derivative **150** was formed in the 5-position. The subsequent cross-coupling reaction gave the desired products **151** with substituted aryl halides as well as some heteroaryl halides (Scheme 50). Cross-coupling with aryl iodides gave good yields (67–88%), but poor results were observed with aryl bromides. In the case of 4-bromoacetophenone, the desired compound was isolated in only 26% yield, while the reaction failed completely with 2-bromobenzaldeyde, only providing a complex and inseparable mixture. Good yields, however, were reported for 1-bromonaphthaline (83%). Heterocyclic halides gave mediocre to good yields in this reaction, 2-bromopyridine (68%) giving the highest and 5-bromoindole (26%) the lowest yield. The same halides were also applied successfully to Negishi cross-coupling with 2-thiazolylzinc chloride.[110]



Scheme 50.

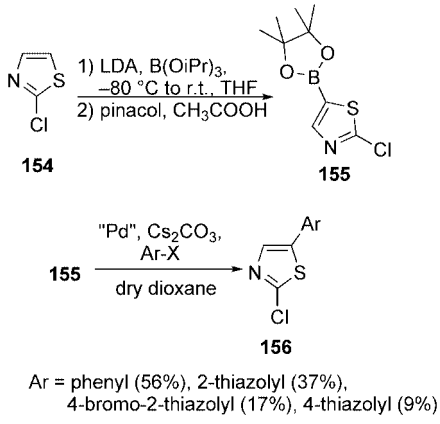
A copper-catalyzed Negishi reaction towards 2,2′-bibenzo[*d*]thiazole derivative **153** was reported recently (Scheme 51).[111]



Scheme 51.

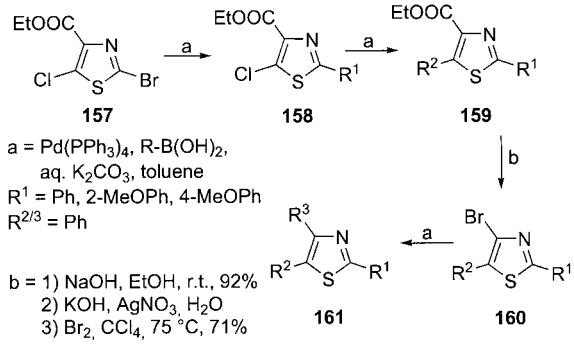
4.2. Suzuki–Miyaura Reaction

So far, Suzuki–Miyaura reactions on thiazole have only been reported for the conversion of halothiazoles with various boronic acids. Although the preparation of 2-thiazoleboronic acid has been claimed in a few patents,[112–114] actual success appears doubtful on the basis of recent studies within our research group.[115] We found that free boronic acids were not stable in the thiazole series due to rapid deboronation. On the other hand, we succeeded in the preparation of the first thiazoleboronic acid ester **155** and successfully applied it in Suzuki–Miyaura reactions (Scheme 52). It has to be mentioned that absolutely dry conditions were necessary in the cross-coupling step towards **156** to avoid hydrolysis of the ester followed by deboronation of the acid. Still, yields were low, and the method needs further improvement. Nevertheless, it might become a useful alternative to the use of toxic tin compounds in Stille reactions.[115]



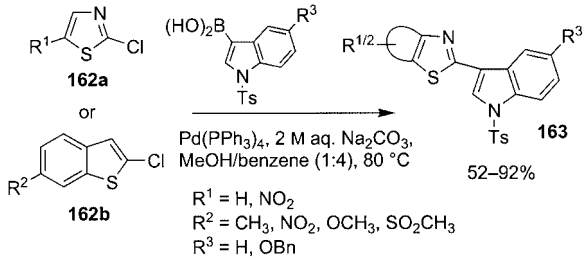
Scheme 52.

Selective reaction at the 2- and 5-positions was investigated in recent studies: Initially, the more reactive 2-position of **157** was cross-coupled with aromatic boronic acids under standard Suzuki–Miyaura conditions in good yields (76–92%). Small amounts of debrominated starting material and dechlorinated cross-coupling product were observed as byproducts. Subsequently, cross-coupling in the 5-position of intermediate **158** was achieved under similar conditions but with prolonged reaction times, and an excess of the organometallic reaction partner was required. Good results (87%) were obtained for the Suzuki–Miyaura example with phenylboronic acid. The ester functionality was then transformed to bromine in two steps (**160**, 67%). Cross-coupling of the 2,5-diphenyl starting material (1 equiv.) into the 4-position with phenylboronic acid gave the desired 2,4,5-triphenylthiazole **161** in 94% yield after 2 hours (Scheme 53). In all three positions, one example for a Stille- [with tributyl(vinyl)stannane], a Negishi- (with 2-pyridylzinc bromide), and a Sonogashira reaction (with phenylacetylene) was reported. The Stille- (72–91%) and the Negishi reaction (70–75%) worked well in all three positions. The Sonogashira reaction was a little troublesome, giving only 19% in 2-, 56% in 5-, and 61% yield in the 4-position.[116,117]



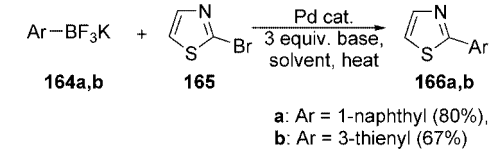
Scheme 53.

Chlorine in the 2-position can be used as the halide instead of bromine. 2-Chlorothiazoles and 2-chlorobenzothiazoles **162a/b** have been used in the Suzuki–Miyaura reaction with indoleboronic acids, and high yields of **163** were obtained (Scheme 54). The efficiency of the reaction was not affected by neutral (CH_3) or electron-withdrawing (NO_2) substituents on the benzothiazole system, but was essentially inhibited by MeO and $MeSO_2$ groups.[118]



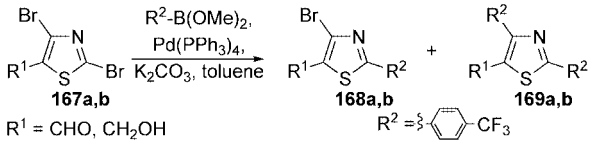
Scheme 54.

In another interesting example, potassium 1-naphthyltrifluoroborate (**164a**) or potassium 3-thienyltrifluoroborate (**164b**) was used in a Suzuki–Miyaura reaction. In both cases, good yields of **166** were obtained in the cross-coupling reaction with 2-bromothiazole (**165**) (Scheme 55). A number of other halides were employed in the reaction and showed similar good results.[119]



Scheme 55.

Other cross-coupling examples of arylboronic acids with 2-bromothiazole or 2-bromobenzothiazoles were reported in the literature.[120,121] Recently, Suzuki–Miyaura cross-coupling of 2,4-dibromothiazole-5-aldehyde **167a** and 2,4-dibromo-5-thiazolemethanol **167b** have been reported. As expected, the latter compound showed a better selectivity between the 2- and 4-positions. The aldehyde gave a mixture of mono- and disubstituted derivatives accompanied by unreacted starting material. When the hydroxymethyl compound was used, optimized reaction conditions afforded the 2-substituted product in 87% yield (Scheme 56). The Stille reaction gave similar selectivity; however, the yield was lower (68%).[122]

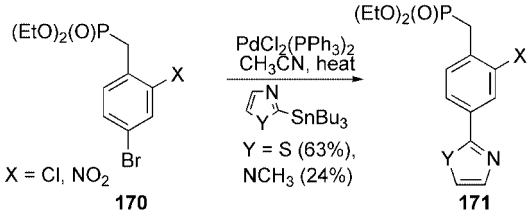


Scheme 56.

4.3. Stille Reaction

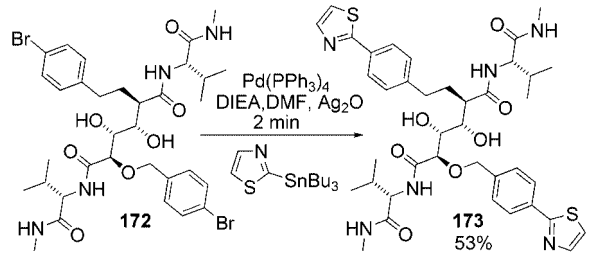
As in the case of the previously discussed heterocyclic systems, the Stille reaction is also the most common cross-coupling reaction in thiazole chemistry. All three possible stannanes have been prepared and used in a number of cross-coupling experiments. Additionally, various halothiazoles or triflates have been used in the Stille reaction. A number of examples with 2-stannylthiazoles were reported in the literature starting from very simple transformations up to cross-coupling reactions on complex substrates. The Stille reaction is highly tolerant towards a wide range of functional groups. Selected examples are presented in the following schemes.

Bromobenzene **170** was treated with 2-(tributylstannyl)-thiazole in the presence of diethyl phosphonate and a nitro or chloro group to yield 63% of **171**.[123] Other heterocyclic stannanes showed similar results in the reaction, including imidazole (24%) (Scheme 57).



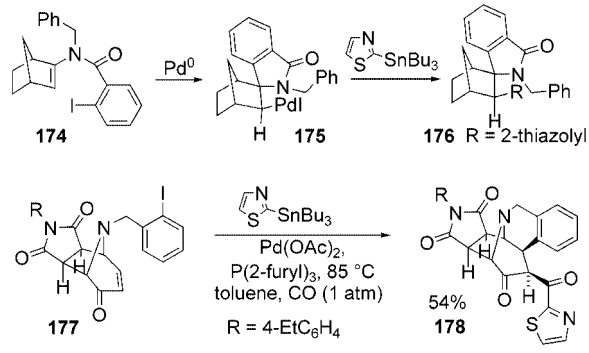
Scheme 57.

In the course of the synthesis of potent C_2-symmetric P1/P1′-modified HIV-1 protease inhibitors, the two bromines of **172** were both cross-coupled with (2-tributylstannyl)thiazole in 53% yield to **173**.[124] The amide and hydroxyl groups in the starting material did not require protection and had no impact on the efficiency of the coupling reaction (Scheme 58).



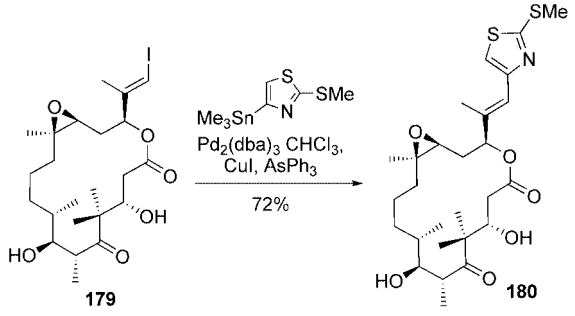
Scheme 58.

An interesting Pd-catalyzed tandem cyclization–anion-capture process was reported by Grigg and co-workers.[125] Spiro-intermediate **175** is formed in the initial step of the sequence from **174**. In a second step, (2-tributylstannyl)thiazole reacts with this intermediate to introduce the thiazole ring. Later, the method was extended by a carbonylation reaction in the metal-catalyzed process (Scheme 59).[126]



Scheme 59.

The use of 4-(tributylstannyl)thiazoles in Stille cross-coupling reactions is well-established. It proved to be very efficient in the synthesis of epothilones and their analogs (e.g. **180** from **179**) (Scheme 60).[127]

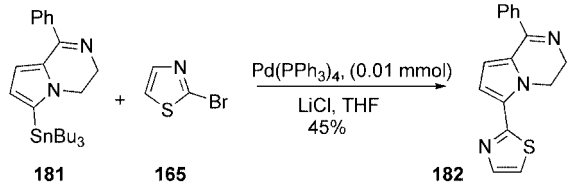


Scheme 60.

A similar method was reported in the total synthesis of WS75624 B, a natural product isolated from the fermentation broth of *Saccharothrix* sp. no. 75624.[128] Additionally, the synthesis of cystothiazoles was accomplished by using the Stille methodology as an alternative to the earlier re-

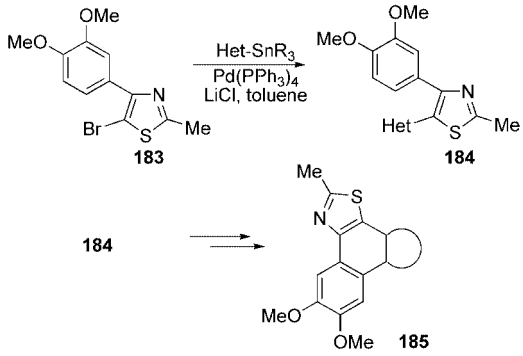
ported Negishi approach.[129] The yield in the bithiazole formation step was lower in the Stille reaction. In this case, the 2,4-bis(triflate) of thiazole instead of 2,4-dibromothiazole was used as the electrophile.

Thiazoles were also applied in Stille reactions as halides. Low catalyst loadings could be applied in the cross-coupling of 2-bromothiazole **165** with 1-phenyl-6-(tributylstannyl)-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**181**), giving 45% of the desired product **182** (Scheme 61).[130]



Scheme 61.

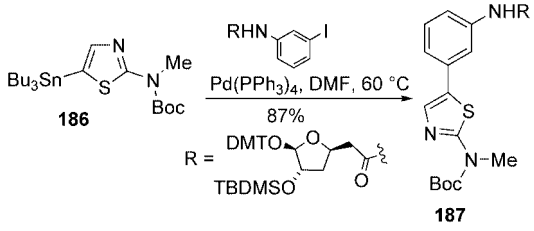
A more complex halothiazole was applied in the course of studies towards phenanthro- and phenanthroid fused thiazoles (**185**, Scheme 62). The bromothiazole **183** was formed by cyclization and subsequent direct bromination in the free 5-position. This bromide was then used in a Stille reaction with a series of heterocyclic stannanes to give compounds **184** in 69–89% yield.[131]



Het = 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridinyl, 3-pyridinyl, 6-methoxy-2-pyridinyl, 6-methoxy-3-pyridinyl, N-methyl-2-pyrrolyl

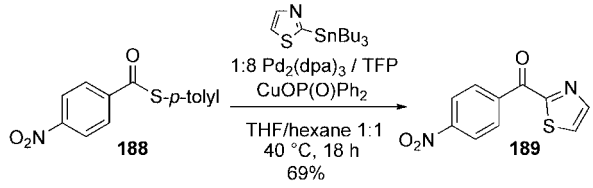
Scheme 62.

A complex example for the cross-coupling of 5-(tributylstannyl)thiazole **186** was reported.[132] Compound **186** was subjected to a Stille reaction with a highly functionalized iodobenzene derivative to give the modified nucleoside precursor **187** in excellent 87% yield (Scheme 63).



Scheme 63.

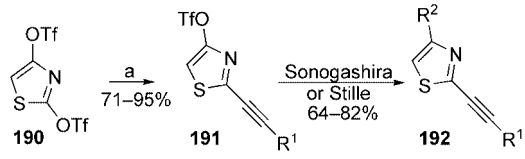
2-(Tributylstannyl)thiazole was also used for ketone formation by the Stille method. Thiol ester **188** served as activated precursor, and 69% of the desired compound **189** was obtained (Scheme 64). Besides 2-(tributylstannyl)thiazole, a number of other stannanes were applied to this reaction, and yields of 61–97% were obtained.[133]



Scheme 64.

4.4. Sonogashira Reaction

Especially 2-bromothiazoles have been used in the Sonogashira reaction. With simple 2-bromothiazole, moderate to good yields have been reported with a number of different alkynes by using conventional catalyst systems[134–136] or the relatively new Tedicyp [all-*cis*-1,2,3,4-tetrakis(diphenylphosphanylmethyl)cyclopentane] ligand.[137] The Sonogashira reaction of 4-bromothiazoles was also reported for example in the synthesis of epothilone C analogs.[138] Additionally, selective cross-coupling reactions on thiazole-2,4-bis(triflate) **190** were reported (Scheme 65). The first Sonogashira reaction took place exclusively in the 2-position to give compounds **191**. The triflate in the 4-position was then used for a second Sonogashira or Stille cross-coupling reaction.[99]



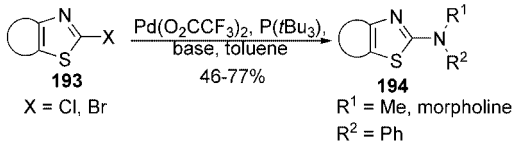
a: $Pd(PPh_3)_4$, CuI, 2,6-lutidine, alkyne, DMF, r.t.
R^1 = -$(CH_2)_2$Ph, -CH_2OBn, -CH_2OTBS, -CH_2NHCOOMe
R^2 = -Me, -$CH_2CH{\equiv}CH_2$, -C≡C-CH_2OTBS, -C≡C-CH_2-NH(COOMe), 4-Me-thiazol-2-yl

Scheme 65.

4.5. Other Methods

4.5.1. C–N Bond Formation

Besides C–C cross-coupling reactions also C–N cross-coupling reactions were reported. By using $Pd(O_2CCF_3)_2$/$P(tBu_3)$ as the catalytic system, 2-bromothiazole and 2-chlorobenzothiazole were cross-coupled with various amines (morpholine, $HNBu_2$, HNMePh) in 46–77% yield (Scheme 66).[139]

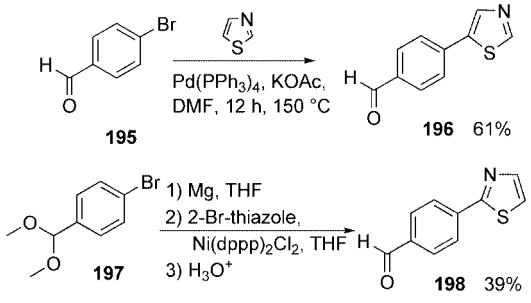


Scheme 66.

Pyridin-2(1*H*)-one was C–N cross-coupled with several heterocyclic bromides. 2-Bromothiazole afforded 27% of the desired product. Only bromothiophenes gave high yields in this CuI-catalyzed reaction.[140]

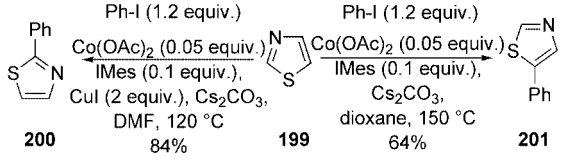
4.5.2. C–H Activation

An interesting example without an organometallic precursor was reported recently. Thiazole was selectively substituted in the 5-position using 4-bromobenzaldehyde **195** as electrophile. On the basis of NMR data, substitution of the thiazole in the 4-position was ruled out, and **196** was obtained selectively. The isomeric 2-substituted thiazole **198** was prepared by a Ni-catalyzed Kumada–Corriu–Tamao reaction (Scheme 67) from thiazole and **197**.[141]



Scheme 67.

This approach was further developed, and a method to selectively arylate the parent thiazole either in the 2- or 5-position depending on the applied reaction conditions was reported.[142] The choice of solvent proved to have a significant influence on the reaction. Arylation in the 2-position to **200** was only achieved when CuI was used as additive. Without CuI, **201** was formed. In both cases, the strong electron donor IMes was used as ligand with $Co(OAc)_2$ as metal source (Scheme 68).



Scheme 68.

4.5.3. Iron-Catalyzed Cross-Coupling

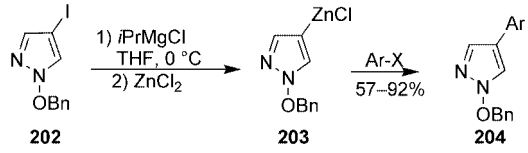
In recent years, iron-catalyzed cross-coupling reactions were developed and in one example also applied in thiazole chemistry. 2-Chlorobenzothiazole was cross-coupled with *n*-$C_{14}H_{29}MgBr$ to the corresponding product in 68% yield. The reaction was carried out in THF/NMP by using $Fe(acac)_3$ as catalyst.[143]

5. Pyrazole

N-Protected 4-iodopyrazoles have frequently been used in cross-coupling reactions. They were used both as halides and as precursors for the formation of organometals either by lithiation or via the corresponding Grignard intermediates. Methods applied include the Kumada–Corriu, Stille, and Negishi protocol.

5.1. Negishi Reaction

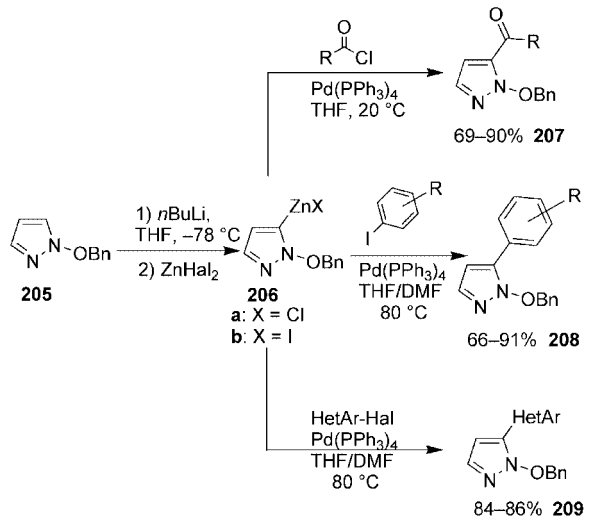
Negishi cross-couplings are well established in pyrazole chemistry. 1-(Benzyloxy)-4-iodopyrazole (**202**) was metalated by using *i*PrMgBr. Subsequent addition of $ZnCl_2$ and Negishi cross-coupling of intermediate **203** with aryl- and heteroaryl iodides gave the corresponding products **204** in good to excellent yields (57–92%) (Scheme 69). The reaction worked well with both electron-donating and electron-withdrawing substituents. Experiments applying 1-(benzyloxy)-4-(tributylstannyl)pyrazole (prepared via pyrazolylmagnesium bromide) in a Stille reaction or the Grignard intermediate directly in a Kumada–Corriu reaction failed.[144,145] The pyrazolylzinc chloride was also used for $Pd(PPh_3)_4$-catalyzed cross-coupling with acid chlorides but afforded the corresponding acylation products in low yields (20–43%). In this case, the corresponding tributylstannyl derivative proved to be more reactive, and yields >70% were reported for the majority of the experiments.[146]



Scheme 69.

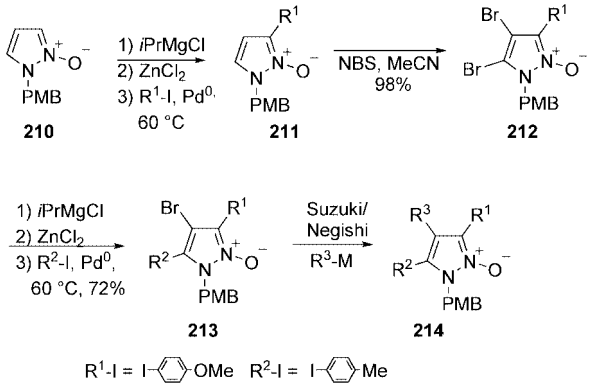
Cross-coupling reactions of zinc organyls **206a**,**b** in the 5-position with acid chlorides (to **207**), aryl halides (to **208**), and hetaryl halides (to **209**) were accomplished in generally good yields (Scheme 70).[147] However, in another comparative study using direct metalation instead of metal–halogen exchange, the Stille method gave better results (56%) relative to the Negishi protocol (20%) also for reactions in the 5-position.[148]

2-(4-Methoxybenzyl)pyrazole-1-oxide (**210**) was cross-coupled in all three carbon positions. The pyrazolylzinc chloride was prepared in the 5-position by metalation with *i*PrMgCl and quenching with $ZnCl_2$. In a subsequent cross-coupling with 4-iodoanisole by a standard Negishi method a 95% yield of **211** was obtained. When *n*BuLi was used instead of *i*PrMgCl, only 56% product was obtained after cross-coupling. Subsequent bromination with NBS afforded the corresponding 3,4-dibromopyrazole **212** which underwent a second selective Negishi cross-coupling in the 3-po-



Scheme 70.

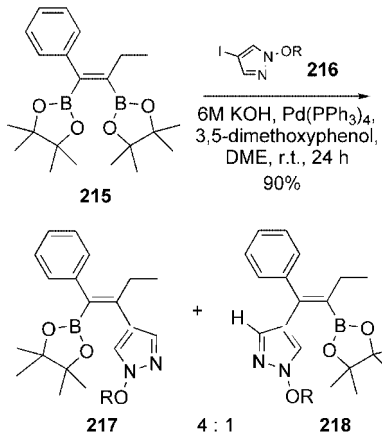
sition to **213** (Scheme 71). The remaining bromine in the 4-position of **213** was finally used either for a third Negishi reaction with 4-fluoroiodobenzene (64%) or 4-iodonitrobenzene (72%), or a Suzuki–Miyaura reaction with 4-fluorophenylboronic acid (66%) to give compounds **214**.[149]



Scheme 71.

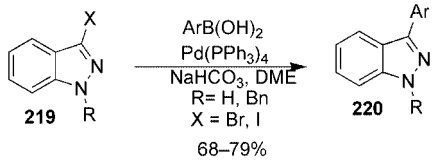
5.2. Suzuki–Miyaura Reaction

Again, pyrazoles were only applied as halides in the Suzuki–Miyaura reaction. The formation of a pyrazoleboronic acid was reported in the literature in 51% yield, but no cross-coupling example was presented.[150] Both 4- and 5-iodopyrazoles (in Scheme 72 4-iodopyrazole **216** is presented) have been used in Suzuki–Miyaura reactions with alkenylboronic acid esters in the course of the preparation of tamoxifen analogs.[151] The cross-coupling reaction with **215** proceeded in high overall yields (90%) and a C1/C2 regioselectivity of 4:1 (**217**/**218**) was observed (Scheme 72). The second boronic ester functionality was used for a second cross-coupling reaction with aryl- or heteroaryl iodides.



Scheme 72.

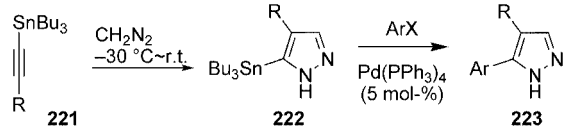
Suzuki–Miyaura reactions have been reported also in the free 3-position of indazole derivatives **219**. Under standard cross-coupling conditions, good yields were reported especially when an N-benzylated starting material was applied. Four different phenylboronic acids were subjected to the cross-coupling reaction as well as 2-furyl- and 2-thienylboronic acid. Yields of 68–79% of **220** were reported when iodide was used as leaving group. Bromine gave significantly lower yields (Scheme 73).[152] Other examples can be found in the literature.[153]



Scheme 73.

5.3. Stille Reaction

3-Stannylpyrazoles **222** can be formed by cyclization of diazomethane and alkynylstannanes **221**. The tributylstannyl group was then further used for Stille cross-coupling to compounds **223** with various aryl halides (Scheme 74).[154,155]



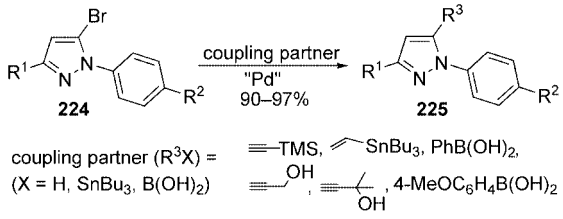
Ar-X	Yield
2,4-Me_2PhI	94%
2-ClPhI	89%
2-(CO_2Me)PhI	83%
3-(MeO)PhI	74%
4-(MeO)PhI	59%
4-(NO_2)PhI	84%
4-AcPhBr	trace
2-Br-5-(NO_2)pyridine	35% (GC)
5-Br-pyridine	0

Scheme 74.

Alternatively to a cyclization approach, the Bu_3Sn group can also be introduced by lithiation and subsequent electrophilic quenching with Bu_3SnCl. A 4-(tributylstannyl)pyrazole was prepared by this method and subsequently cross-coupled with four *p*-substituted aryl iodides. Electron-donating substituents worked well (4-MeO-PhI 55%, 4-HO-PhI 90%, 4-H_2N-PhI 86%), but conversion with 4-O_2N-PhI as electrophile failed.[156] The method was also applied in the formation of 3-, 4-, and 3,4-bis(tributylstannyl)pyrazoles. The Pd-catalyzed cross-coupling with an acid chloride was reported in one example in 69% yield, and also silyl groups were introduced by this method.[157]

5.4. Sonogashira Reaction

Bromo- and iodopyrazoles have been applied in Sonogashira cross-coupling reactions, e.g. 1,3-disubstituted-5-bromopyrazoles **224** were cross-coupled with various alkynes as well as with stannanes and boronic acid esters (Scheme 75). Excellent yields of compounds **225** in a range of 90–97% were generally achieved.[158]

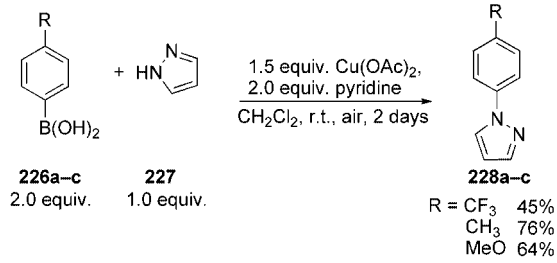


Scheme 75.

Additionally, 3-, 4-, and 5-iodopyrazoles have been investigated in the Sonogashira and the Stephens-Castro reaction by using copper acetylides.[159,160] The latter was found to be a convenient method for the preparation of (*N*-acetylamino)alkynylpyrazoles, whereas the Sonogashira method was troublesome in cases of alkynes bearing electron-donating substituents. Neither 3- nor 5-iodopyrazoles reacted in the standard Sonogashira protocol, and reductive deiodination accompanied by homo-coupling of the 1-alkyne component was the predominant reaction with 4-iodo derivatives. Only alkynes bearing electron-withdrawing substituents gave smooth conversions. A method for successful cross-coupling of 2-propyn-1-ol with 4-iodopyrazoles was later established. A critical improvement was the application of two equivalents of PPh_3 to regenerate the precipitated metallic Pd as active catalyst in order to obtain satisfactory results.[161]

5.5. C–N Bond Formations

A copper-catalyzed C–N-bond-forming cross-coupling reaction with phenylboronic acids **226a–c** was reported to give 1-aryl-substituted pyrazoles **228a–c** in moderate to good yields (Scheme 76).[162,71] Alternatively to boronic acids, aryl halides can directly be applied in C–N bond formation, and usually high yields are obtained (≈ 90%); however, long reaction times are necessary (24–90 hours).[163,74]



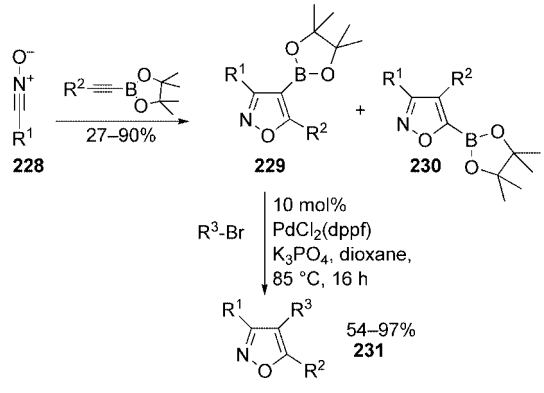
Scheme 76.

6. Isoxazole

Compared with the so far discussed azoles, fewer cross-coupling examples have been reported in isoxazole chemistry. This might be attributed to the lack of prominent target compounds containing an isoxazole structural motif.

6.1. Suzuki–Miyaura Reaction

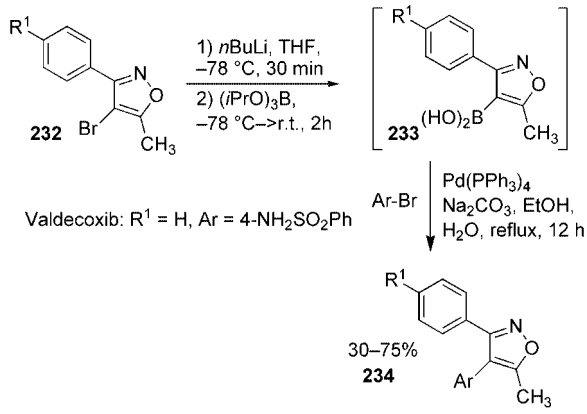
The Suzuki–Miyaura reaction was reported in isoxazole chemistry using the heterocycle as halide as well as boronic acid (or ester). In these cases, the organoboranes were not synthesized by a metalation-quenching strategy but directly introduced through cyclization of nitrile oxides **228** and alkynylboronic acid esters. In the cyclization reaction, two regioisomers bearing the boronic acid ester in the 4- or 5-position (**229** or **230**) can be formed. Methods were reported with good control of the regiochemistry in the final product depending on the substituents in the starting material. Subsequent cross-coupling of the isoxazole-4-boronic acid ester gave the products **231** in up to 97% yield; however, only few examples were reported (Scheme 77).[164,165]



Scheme 77.

A single report is available where a boronic acid was introduced in the 4-position of **232** by a lithiation strategy; however, no isolated yields were reported. The crude boronic acids **233** were used successfully in Suzuki–Miyaura reactions under standard conditions to give valdecoxib and some isomers in moderate to good yields (**234**: 30–75%, Scheme 78).[166] 4-Bromoisoxazole was also used as halide

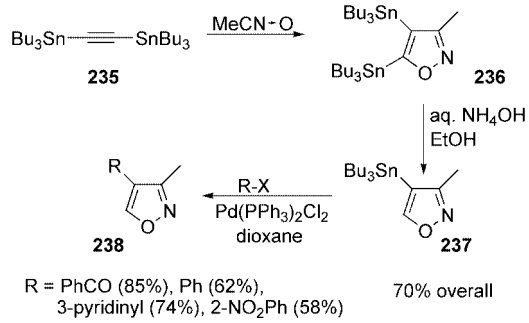
in the cross-coupling reaction with commercially available boronic acids in 10–65% yield. Other examples illustrating haloisoxazoles in Suzuki–Miyaura reactions were reported.[167,168]



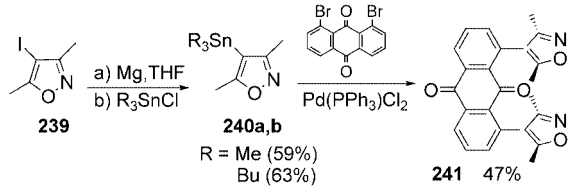
Scheme 78.

6.2. Stille Reaction

(Tributylstannyl)isoxazole **237** can be accessed by 1,3-dipolar cycloaddition of bis(tributylstannyl)acetylene (**235**) with nitrile oxides. The initially obtained 4,5-distannane **236** was further transformed to the 4-stannyl compound **237** by basic hydrolysis and subsequently used in the Stille reaction with benzoyl chloride (85%) or aryl halides (58–74%) (Scheme 79).[169]



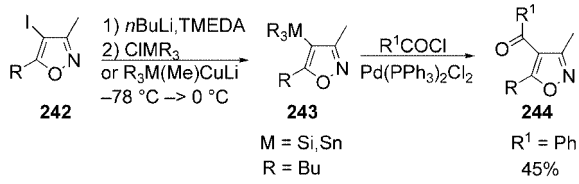
Scheme 79.



Scheme 80.

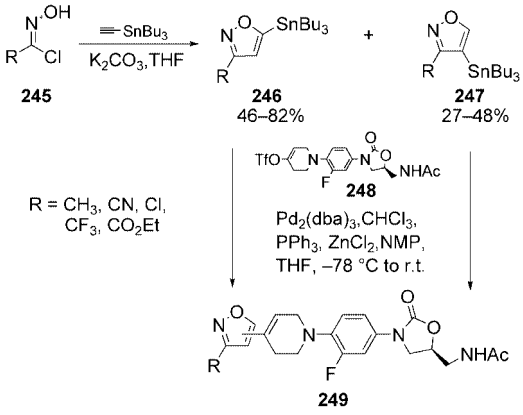
Alternatively, 4-(trialkylstannyl)isoxazoles **240a**,**b** were prepared by a Grignard reaction from 3,5-dimethyl-4-iodoisoxazole (**239**). The subsequent cross-coupling with dibromoanthraquinone and -anthracene to **241** proceeded in moderate yields (30–47%) (Scheme 80).[170]

3,5-Dimethyl-4-(tributylstannyl)isoxazole (**243**, M = Sn) has also been prepared by lithiation and subsequent quenching with Bu_3SnCl (72%).[157] In this case, cross-coupling with benzoyl chloride gave 45% yield of **244** (Scheme 81).

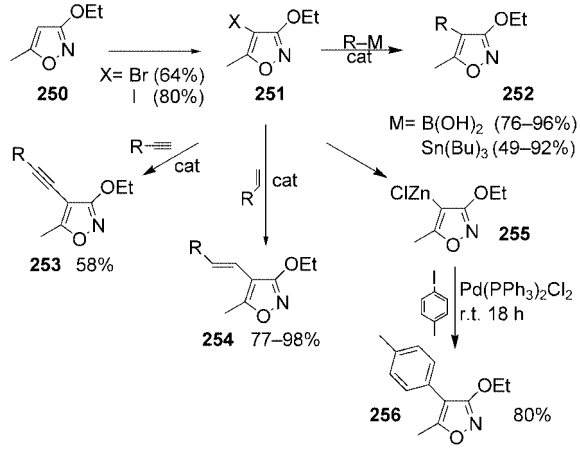


Scheme 81.

A mixture of 4- and 5-(tributylstannyl)isoxazole (**246** and **247**) was obtained by cyclization of tributyl(ethynyl)stannane and various substituted chlorooximes **245**. Subsequent cross-coupling with triflate **248** gave novel antibacterial agents **249** (52–93%) (Scheme 82).[171] Alternatively, nitrile oxides can be directly used as reaction partners in the cyclization.[154]



Scheme 82.



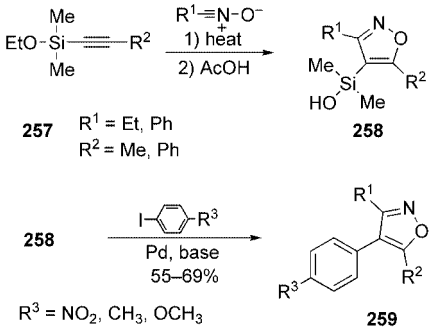
Scheme 83.

A number of examples have been reported where isoxazole halides **251** were cross-coupled with various stannanes or other organometallic compounds. 4-Bromo and 4-iodoisoxazoles were successfully used in Sonogashira (to **253**), Heck (to **254**), Negishi (to **256**), Stille, and Suzuki–Miyaura reactions (to **252**).[172] As expected, iodo reagents gave better results (Scheme 83).

A similar set of examples was reported for 5-iodo-3-(2-pyridinyl)-isoxazole and a comparative study of Sonogashira, Suzuki-Miyarua, Negishi, and Stille protocols gave generally high yields (80–94%).[173]

6.3. Hiyama Reaction

Since the C–Si bond is less polarized than the carbon–metal bonds of other metal organyls, fewer cross-coupling examples with silicon organyls were reported until now. One successful example was reported very recently on isoxazole. The starting material **258** was prepared by a [3+2]cycloaddition from **257**, in which the compound bearing the silicon group in the 4-position was predominantly formed and was accompanied by considerable amounts of the 5-isomer. Compounds **258** were cross-coupled with iodobenzenes to give the cross-coupling products **259** in 55–69% yield (Scheme 84).[174]

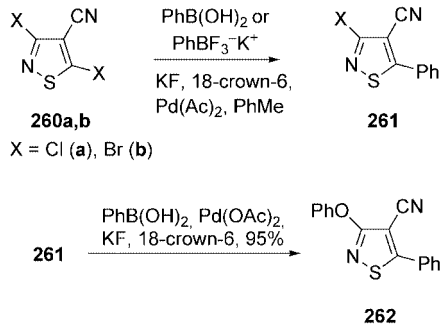


Scheme 84.

7. Isothiazole

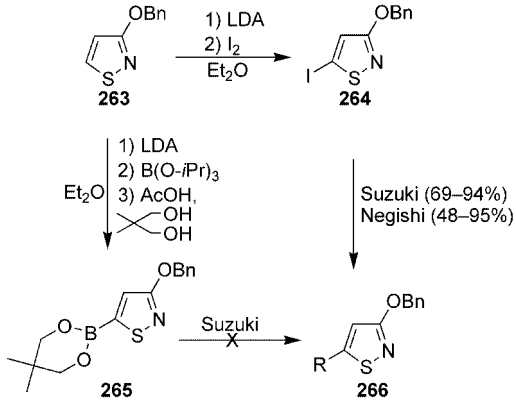
With respect to cross-coupling methodology, isothiazoles have been investigated only on very few occasions so far.

Suzuki–Miyaura reactions using chloro-, bromo-, and iodoisothiazoles have been reported. The cross-coupling of 3,5-dichloroisothiazole-4-carbonitrile (**260a**) with a range of benzeneboronic acids was optimized, and often yields >90% were obtained. The cross-coupling reaction took place selectively in the 5-position (**261**). The possibility of using $PhBF_3^-K^+$ instead of $PhB(OH)_2$ was also investigated, and optimized reaction conditions gave 99% yield. The same result was obtained when the dibromo compound **260b** was used as starting material. Subsequent cross-coupling in the 3-position was attempted with phenylboronic acid but did not give the desired compound. Instead, 3-phenoxy-5-phenylisothiazole-4-carbonitrile (**262**) was formed (Scheme 85). It was reasoned that phenol was formed from the boronic acid followed by a nucleophilic exchange reaction of the halide in the 3-position leading to this unexpected result.[175]



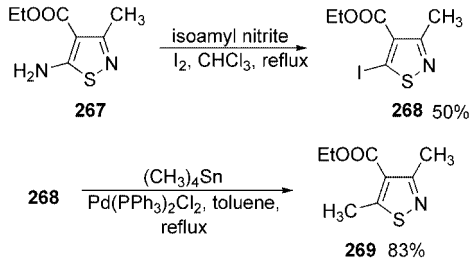
Scheme 85.

5-Iodoisothiazole **264** was used in the Suzuki–Miyaura and Negishi reactions. Phenylboronic acid (82%) and a number of heterocyclic boronic acids or esters were applied and gave good to excellent yields (69–94%) of compounds **266**. Alternatively, the boronic acid ester **265** was formed in the 5-position of the isothiazole by lithiation and subsequent quenching with $B(OiPr)_3$ followed by transesterification. Compound **265** could not be successfully applied in a Suzuki–Miyaura reaction, and only deboronation was observed. In the same contribution, three examples were also performed by the Negishi strategy; again the isothiazole was applied as the halide component. For the transformation with phenylzinc chloride, the yield (95%) was better than that in the Suzuki–Miyaura reaction, but the other two examples gave considerably lower yields (2-thienyl 63%, 2-pyridinyl 48%) (Scheme 86).[176]



Scheme 86.

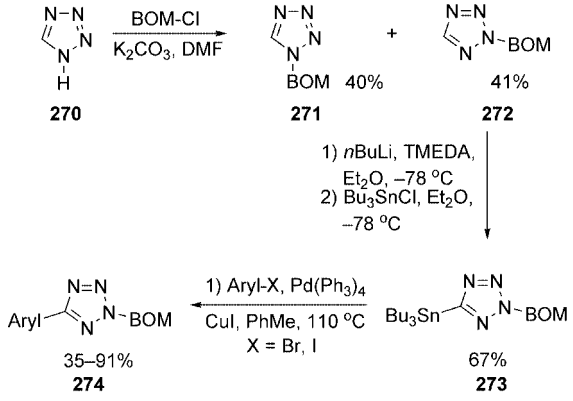
In one example, a methyl group was introduced into the 5-position of isothiazole by a Stille reaction, although the authors refer to the method as the Castro–Stephens reaction.[177] Commercially available starting material **267** was transformed into the corresponding iodide **268**. Subsequent Pd-catalyzed reaction with Me_4Sn gave the desired compound **269** in 83% yield (Scheme 87).



Scheme 87.

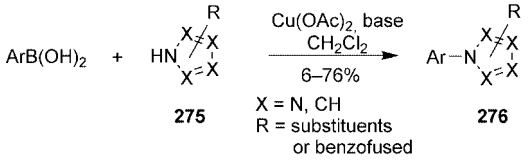
8. Azoles Containing Three or More Heteroatoms

Cross-coupling chemistry on azoles containing more than two heteroatoms has hardly been studied up to now. For thiadiazoles and oxadiazoles no examples at all were published in recent years. Tetrazole **273** was applied in a Stille cross-coupling reaction in the 5-position. After N-protection of **270** to regioisomers **271** and **272**, the corresponding 5-(tributylstannyl)triazole **273** was formed from **272**. The cross-coupling was then achieved in good yields with a series of carbocyclic as well as heterocyclic electrophiles to give compounds **274** (Scheme 88).[178]



Scheme 88.

Copper-catalyzed C–N-bond-forming reactions were also reported: when 1,2,3- and 1,2,4-triazole were subjected to this protocol, significantly lower yields were obtained (11% and 6%) relative to the imidazole- (62–72%) and pyrazole (45–76%) examples. 5-Phenyltetrazole also gave low yields in this conversion (26%) (Scheme 89).[71]



Scheme 89.

Acknowledgments

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