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# Recent synthetic strategies for the functionalization of fused bicyclic heteroaromatics using organo-Li, -Mg and -Zn reagents†

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This review highlights the use of functionalized organo-Li, -Mg and -Zn reagents for the construction and selective functionalization of 5- and 6-membered fused bicyclic heteroaromatics. Special attention is given to the discussion of advanced syntheses for the preparation of highly functionalized heteroaromatic scaffolds, including quinolines, naphthyridines, indoles, benzofurans, benzothiophenes, benzoxazoles, benzothiazoles, benzopyrimidines, anthranils, thienothiophenes, purine coumarins, chromones, quinolones and phthalazines and their fused heterocyclic derivatives. The organometallic reagents used for the desired functionalizations of these scaffolds are generally prepared *in situ* using the following methods: (i) through directed selective metalation reactions (DoM), (ii) by means of halogen/metal exchange reactions, (iii) through oxidative metal insertions (Li, Mg, Zn), and (iv) by transmetalation reactions (organo-Li and Mg transmetalations with  $\text{ZnCl}_2$  or  $\text{ZnO}(\text{Piv})_2$ ). The resulting reactive organometallic reagents allow a wide range of C–C, C–N and C–X cross-coupling reactions with different electrophiles, employing in particular Kumada or Negishi protocols among other transition metal (Pd, Ni, Co, Cu, Cr, Fe, etc.)-catalyzed processes. In addition, key developments concerning selective metalation techniques will be presented, which rely on the use of RLi, LDA and TMP metal bases. These methods are now widely employed in organic synthetic chemistry and have proven to be particularly valuable for drug development programs in the pharmaceutical industry. New and improved protocols have resulted in many Li, Mg and Zn organyls now being compatible with functionalized aryl, heteroaryl, alkenyl, alkynyl and alkyl compounds even in the presence of labile functional groups, making these reagents well-suited for  $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^2)$ ,  $\text{C}(\text{sp}^2)\text{--C}(\text{sp})$  and  $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$  cross-coupling reactions with fused heteroaryl halides. In addition, the use of some transition metal-catalyzed processes occasionally allows a reversed role of the reactants in cross-coupling reactions, providing alternative synthetic routes for the preparation of fused heteroaromatic-based bioactive drugs and natural products. In line with this, this article points to novel methods for the functionalization of bicyclic heteroaromatic scaffolds by organometallic reagents that have been published in the period 2010–2023.

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† Dedicated to Prof. Bert Maes.

## 1 Introduction

Organometallic reagents (R-M; M = Li, Mg, Zn; R = alkyl, alkenyl, alkynyl, aryl, heteroaryl) are widely used in synthetic organic chemistry and various areas of catalysis.<sup>1–10</sup>

These reagents play an important role in drug discovery and development, in the synthesis of natural products and bioactive compounds,<sup>11–17</sup> as well as in programs dedicated to medicinal and materials chemistry.<sup>18–23</sup> A variety of synthetic methods have been developed for the preparation of organometallic reagents such as organolithium, organomagnesium, and organozinc reagents and their derived cognates. Their potential use



in catalytic applications has been investigated by several leading research groups such as those of Snieckus,<sup>24,25</sup> Knochel,<sup>26–30</sup> Harutyunyan,<sup>31–35</sup> Aggarwal,<sup>36–40</sup> Feringa,<sup>41–44</sup> Marek,<sup>45–50</sup> Mongin,<sup>51–53</sup> Kürti,<sup>54–56</sup> Maes,<sup>57–59</sup> Buchwald,<sup>60</sup> Smith,<sup>61</sup> Li,<sup>62</sup> and others.<sup>63–65</sup> All of these methods most likely utilize one of the following procedures depicted in Fig. 1: (i) directed oxidative metal insertions in the presence of LiCl salts or InCl<sub>3</sub>-Lewis acid (Mg, Zn, Al, Mn, In),<sup>66,67</sup> (ii) halogen-metal exchange reactions (X/M, X = Br, I; M = Li, Mg, Zn, Sm, La, Mn) using Turbo Grignard reagents (i-PrMgCl-LiCl) or other organometallic reagents,<sup>68–72</sup> and (iii) chemo- and regioselective

direct metalations using Knochel-Hauser bases (TMPLi, -Mg and -Zn).<sup>73–75</sup>

In the last two decades, organolithium, magnesium and zinc reagents derived from TMP-H (2,2,6,6-tetramethylpiperidiny) have played an important role in organic synthesis. These organometallic reagents have proven to be very effective as they facilitate the chemo- and regioselective metalation of various aromatic and non-aromatic heterocyclic scaffolds.<sup>73–75</sup> The various alkylamine bases, including TMP-M, R<sup>1</sup>R<sup>2</sup>N-M (M = Li, Mg, Zn; R<sup>1</sup> & R<sup>2</sup> = alkyl) and LDA, are synthesized from commercially available secondary amine sources such as



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TMPH, DIPA and their derivatives employing readily available alkyl lithium reagents. These methods, developed by researchers such as Knochel, Snieckus, Mongin and others, have demonstrated the broad applicability of TMP-bases in numerous catalytic and synthetic transformations.<sup>73–75</sup> Recent reports have repeatedly emphasized the influence of ligands on the reactivity and stability of organometallic reagents. For example, organozinc pivalates (R-ZnOPiv) exhibit higher stability than halogenated organometallic

compounds (RMX, M = Mg, Zn; X = Cl, Br, I). In addition, recent kinetic and mechanistic reports have described that salt-stabilized organozinc pivalates show a significant counterion effect due to –OPiv coordination, making them easy to handle even under an oxygen-containing atmosphere. Since these reagents can be stored with no noticeable degradation or loss of yield for up to 48 h under air, they are ideally suited for various transition metal-catalyzed Negishi cross-coupling reactions.<sup>76–83</sup>



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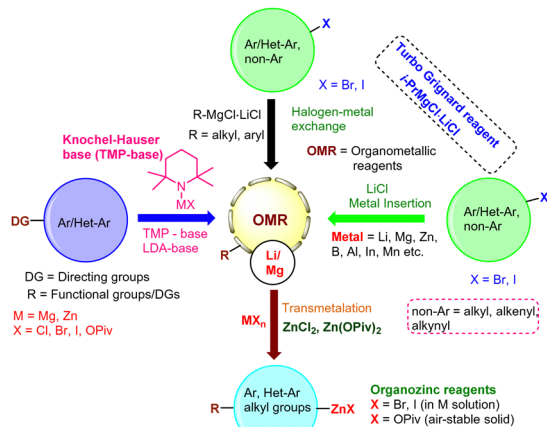


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**Fig. 1** Reported methods for the preparation of organometallic reagents (RMX).

Another major synthetic challenge is the regio- and enantioselective synthesis and functionalization of small organic molecules, as some of these N-heterocyclic systems can serve as chiral ligands or catalysts in synthetic transformations to produce chiral organic intermediates (Fig. 2).<sup>84,85</sup>

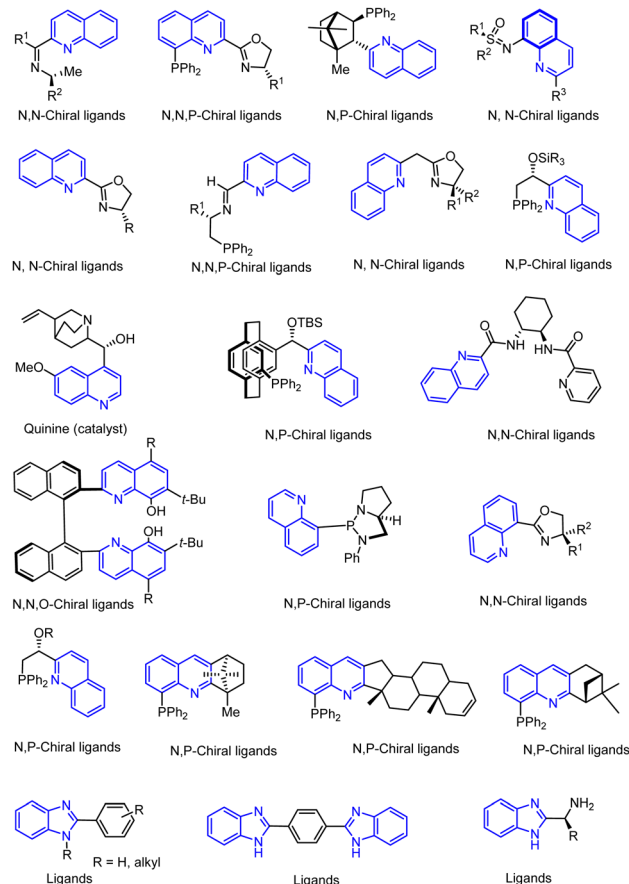
Highly selective and reactive aryl and alkyl organometallic reagents (Li, Mg, Zn) can be attached to electrophilic carbonyl or imine scaffolds to generate complex tetrasubstituted chiral alcohols and amines by catalysis.<sup>86–90</sup> The preferred organometallic compounds for these transformations are organo-Li, -Mg and -Zn reagents, due to their accessibility, low cost and non-toxicity, which favours their use in research laboratories and the pharmaceutical industry. Extensive work has shown that many functionalized fused bicyclic heteroaromatic molecules



**Paul Knochel**

*University in the laboratory of Prof. M. F. Semmelhack. In 1987, he accepted a position as Assistant Professor at the University of Michigan at Ann Arbor, MI. In 1991, he became Full Professor at this university and in 1992, he moved to Philipps-University at Marburg (Germany) as C4-Professor in Organic Chemistry. His research interests include the development of novel organometallic reagents and methods for use in organic synthesis, asymmetric catalysis and natural product synthesis.*

*Paul Knochel has been a full professor for organic chemistry at the Ludwig-Maximilians-University Munich/Germany (LMU) since 1999. He did his undergraduate studies at the University of Strasbourg (France) and his PhD at the ETH-Zürich with Prof. D. Seebach. He spent 4 years at the CNRS at the University Pierre and Marie Curie in Paris with Prof. J.-F. Normant and one year of post-doctoral studies at Princeton*



**Fig. 2** N-Heterocyclic aromatic compounds for use as ligands and catalysts.

are preferred structural motifs, due to their (potential) biological activity. Thus, such compounds are of particular interest for drug development (Fig. 3) but also for the production and modification of novel catalysts, as well as for material science applications.

Such applications require access to substituted scaffolds of diverse heteroaromatic core structures such as quinoline, quinoxaline, naphthyridine, indole, benzofuran, benzimidazole, benzothiophene, benzoxazole, benzothiazole, benzopyrimidine, anthranile, thienothiophene, triazole, purine, coumarin, but also chromones, quinolones and phthalazines.<sup>91–95</sup>

Fused heterocyclic scaffolds have been decorated by various catalytic methods such as metal-free and metal-catalyzed C–H activation reactions, radical transformations, photocatalytic processes, *etc.*<sup>96–98</sup> However, only a few cases require stoichiometric amounts of transition metal catalysts or excess amounts of organometallic reagents to perform these transformations. Moreover, transition metal-catalyzed processes mediated by organometallic reagents can be associated with undesirable side effects, including  $\beta$ -hydride elimination and homocoupling reactions.<sup>99</sup> The functionalization of bicyclic fused heteroaromatic compounds using transition metal catalysts (Co, Fe, Ni, Cr) and organometallic reagents has therefore attracted



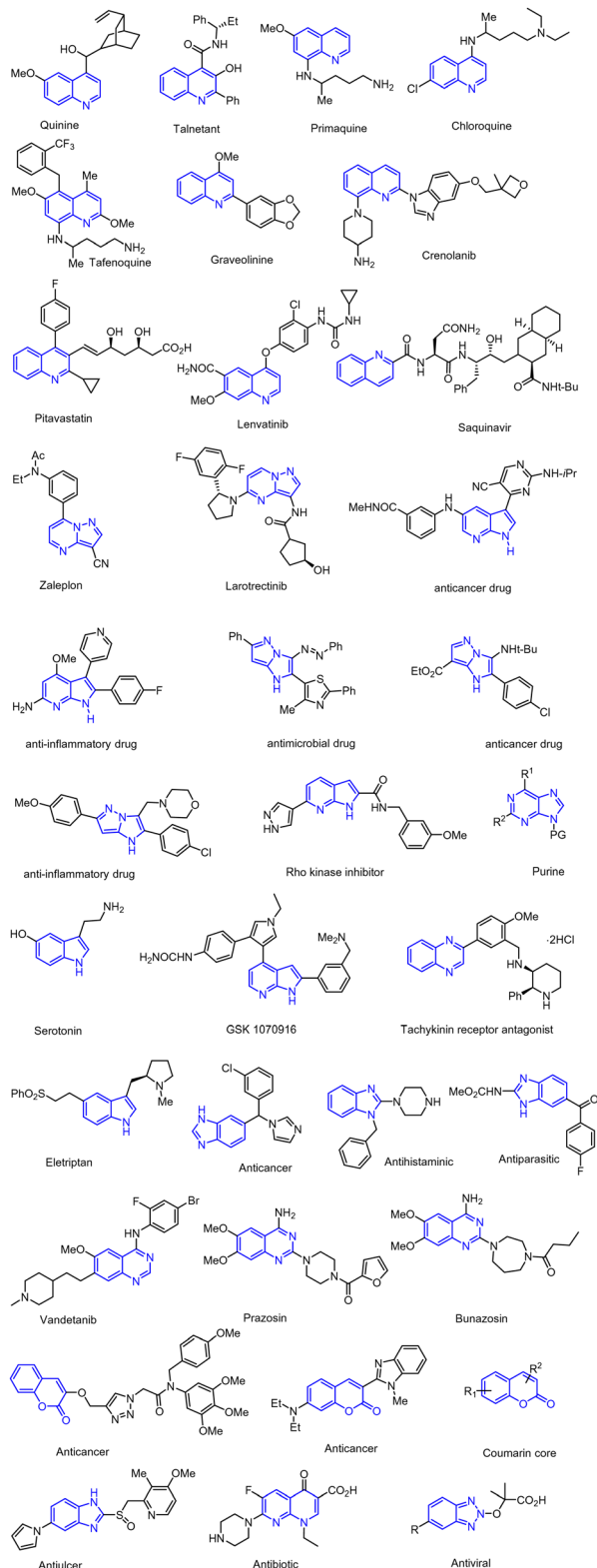


Fig. 3 Selective examples of bicyclic fused heteroaromatic natural products and bioactive compounds.

considerable attention in organic synthesis, particularly in the pharmaceutical industry and sustainable catalysis.

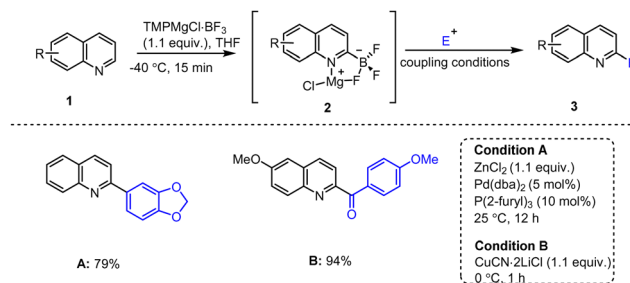
## 2 Functionalization of fused bicyclic hetero-aromatic compounds with TMPLi, -Mg, -Zn

In 2010, one of the best strategies for the functionalization of quinoline scaffolds **1** utilizing  $\text{TMPLi}$ -mediated selective metalations of N-heterocycles was reported by Knochel's group, leading to the preparation of type **2** intermediates.<sup>100</sup> Subsequent transmetalation with  $\text{ZnCl}_2$  (1.1 equiv.) followed by Pd-catalyzed Negishi cross-coupling with aryl iodide afforded the 2-arylated quinoline **3a** in 79% yield. Similarly, a rapid transmetalation of the magnesium species with  $\text{CuCN}\cdot 2\text{LiCl}$  and subsequent acylation reaction with acid chloride led to the corresponding heteroaryl ketone in 94% yield (Scheme 1).<sup>101</sup>

Rohbogner *et al.* developed a method for the preparation of pharmaceutically active quinoline scaffolds such as Talnetant **7** and the P-selectin inhibitor **9** using TMP-M-mediated selective metalations of quinoline derivative **4**. Cross-coupling reactions, deprotection, saponification and amination describe the reaction sequences that provide the expected target quinoline scaffolds **7** and **9** in a few steps under mild conditions and in excellent yields (Scheme 2).<sup>102</sup>

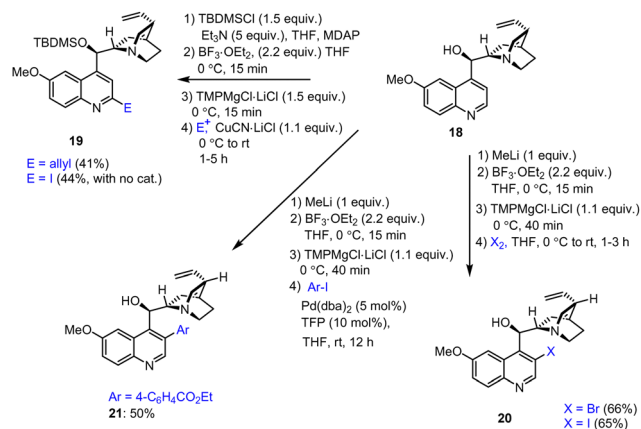
Furthermore, to obtain the reactive magnesium intermediates **11**, many N-heterocyclic phosphorodiamidate derivatives of type **10** including quinoline and quinoxaline molecules were subjected to a directed *ortho*-metalation (DoM) procedure with  $\text{TMPLi}$ -LiCl or  $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ . Later, the resulting organo-metallic reagents **11** were transmetalated with  $\text{ZnCl}_2$  or  $\text{CuCN}\cdot 2\text{LiCl}$  and subsequently reacted with various electrophiles to give the corresponding arylation, acylation, thiolation and allylation products providing *e.g.*, the highly functionalized quinoline and quinoxaline scaffolds **12** in good yields of up to 87% (Scheme 3).<sup>102,103</sup>

A facile and efficient palladium-catalyzed direct benzylation of methylquinoline derivatives using  $\text{TMPZnX}$ -derived bases was accomplished in 2011 by Duez *et al.*<sup>104</sup> The desired zinc-containing quinoline derivatives were prepared by direct  $\text{TMPZnCl}$ -mediated metalations of 2/4-methylquinoline **13** in THF at 25 °C for 1 h. Subsequently, palladium-catalyzed Negishi cross-couplings of the resulting benzylic zinc reagents with a variety of aryl bromides (0.8 equiv.) were performed. When using  $\text{Pd}(\text{OAc})_2$  (2 mol%) and SPhos (4 mol%) as the catalyst, functionalized quinoline scaffolds **15** were obtained in



Scheme 1  $\text{TMPLi}$ -mediated regioselective metalation of quinoline for subsequent cross-coupling reactions.

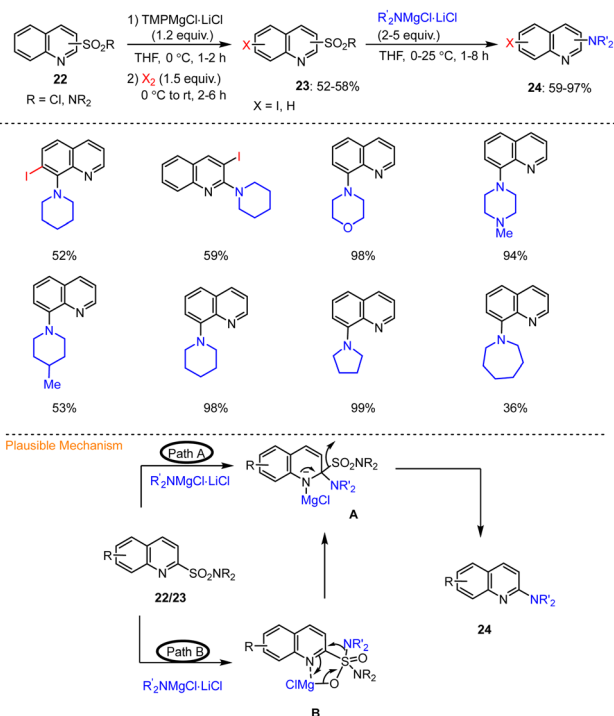




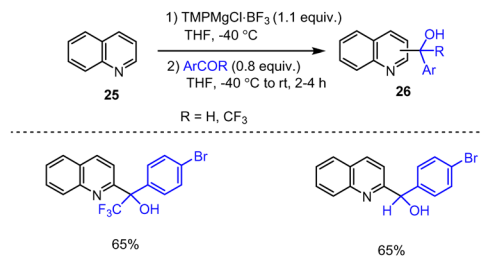
**Scheme 6** C-3- or C-2-Functionalization of quinoline using TMPMgCl·LiCl.

the first step is the selective addition of the magnesium reagents  $R'_2NMgCl \cdot LiCl$  to the  $C=N$  bond of the quinoline skeleton **23**, which leads to the formation of the key intermediate **A**, ultimately providing aminated product **24** after elimination of  $R_2NSO_2MgCl$ . Alternatively, addition of  $R_2NMgCl \cdot LiCl$  to the 2-quinolinylsulfonamide group was proposed first, resulting in species **B**, which can undergo an intramolecular transfer reaction of the amino group to magnesiated intermediate **A**. After elimination, the latter then also affords the desired aminated quinoline **24** (route B, Scheme 7).

Manolikakes *et al.* demonstrated a simple method for the preparation of pyridylmethyl alcohols using TMPMgCl·BF<sub>3</sub>, a



**Scheme 7** Functionalization of quinoline 2- and 8-sulfonamides by TMPMgCl·LiCl followed by desulfonation and addition of  $R_2NMgCl$ .

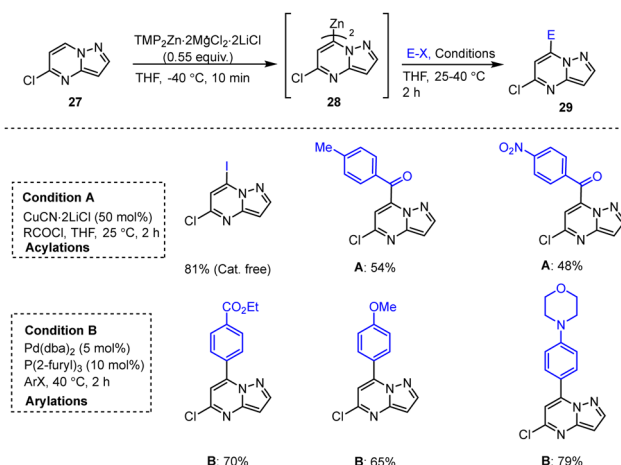


**Scheme 8** Metalation of quinoline followed by 1,2-addition to aromatic aldehydes and ketones.

frustrated Lewis pair that mediates selective metalations to organotrifluoroborates. The latter readily adds to a variety of aromatic aldehydes and ketones in the absence of a transition metal catalyst to afford diarylmethyl alcohols **26** in good yields of 65% (Scheme 8).<sup>108</sup>

Knochel, Zipse and co-workers reported a protocol for the full functionalization of pyrazolo[1,5-*a*]pyrimidine scaffolds **27**, **30**, **33** at positions 2, 3 and 7 using TMP-M bases. Reaction of 5-chloro-pyrazolo[1,5-*a*]pyrimidine with TMPZn under mild conditions afforded heterocyclic zinc intermediates **28**, **31**, **34**. Subsequent reactions with various readily accessible electrophiles in the presence of palladium or copper catalysts afforded the corresponding fused pyrazolo[1,5-*a*]pyrimidine derivatives **29**, **32**, **35** in good to excellent yields (Scheme 9–11).<sup>109</sup> These functionalized heterocyclic compounds are often used in pharmaceutical applications, and the described catalytically active system tolerates both electron-rich and electron-poor functional groups such as Me, SPh, OMe, Cl, I, CN, NO<sub>2</sub>, and CO<sub>2</sub>Et.<sup>110,111</sup>

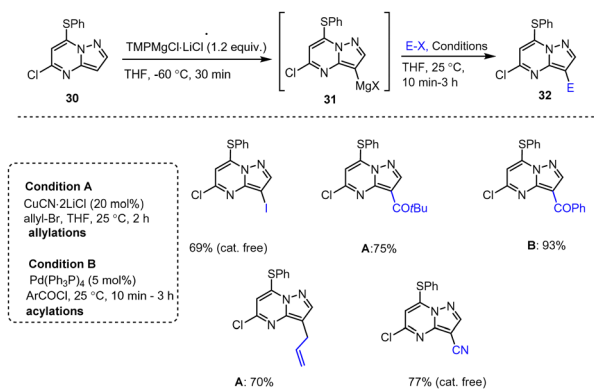
Unsinn *et al.* investigated a simple, mild, and efficient protocol for the regioselective C-3-metallation of 1*H*-indazoles **36** with TMP<sub>2</sub>Zn. The resulting indazolylzinc reagents of type **37** could be smoothly arylated by Pd-catalyzed Negishi cross-coupling reactions in THF at 50 °C with various aryl iodides. The process took 8–24 h to afford the indazolyl analogs **38** in good yields. In addition, copper-mediated acylations and



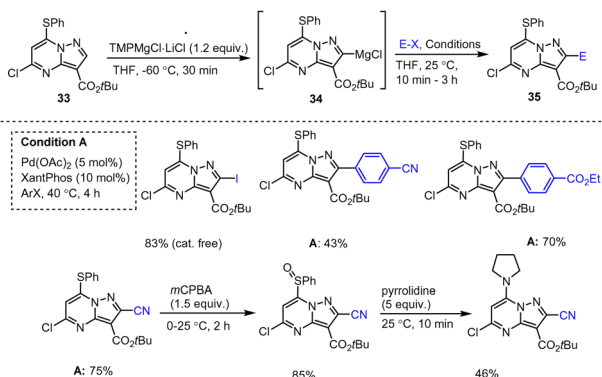
**Scheme 9** Selective zincation at position 7 of the pyrazolo[1,5-*a*]pyrimidine core for subsequent cross-coupling and acylation reactions.







**Scheme 10** Selective C2-metalation of the pyrazolo[1,5-a]pyrimidine scaffold followed by electrophilic trapping reactions.

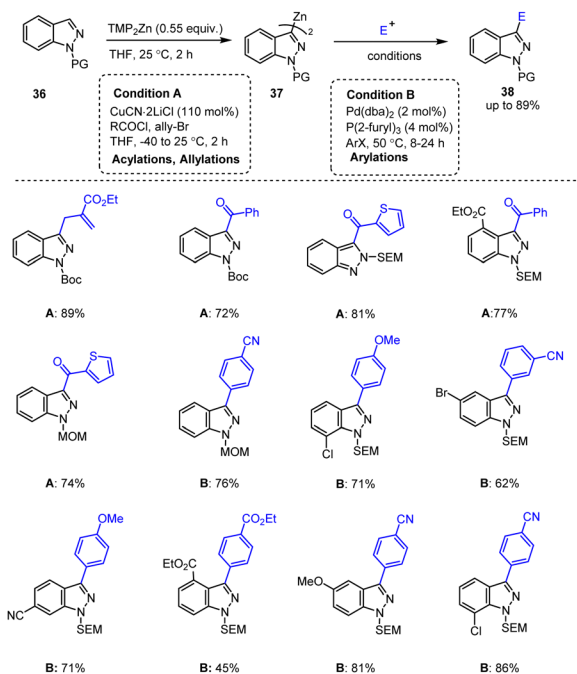


**Scheme 11** Selective metalation of pyrazolo[1,5-a]pyrimidine at 2-position using  $\text{TMPMgCl}\cdot\text{LiCl}$  and quenching with electrophiles.

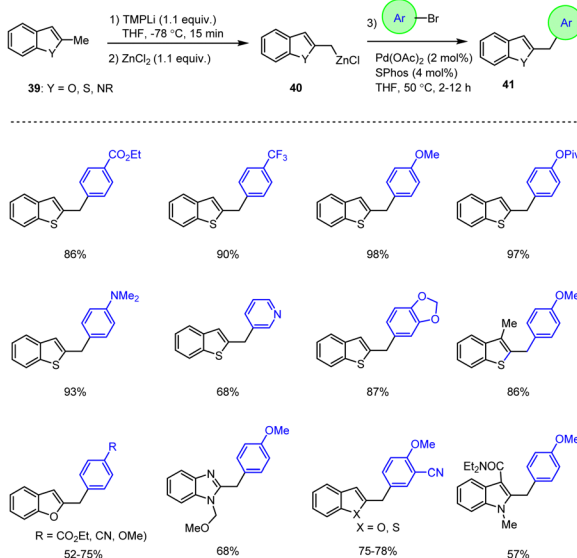
allylations are also applicable under these mild conditions (Scheme 12).<sup>112</sup> This synthetic method is suitable for the preparation of various biologically active N-heterocycles.

In 2012, Duez *et al.* developed an efficient method for the Pd-catalyzed arylation of different 2-methyl-5-membered fused heterocycles of type **39** with  $\text{TMPLi}$  bases. This innovative synthetic process involves  $\text{TMPLi}$ -mediated selective metalation at the benzylic position in THF at  $-78^\circ\text{C}$ , followed by transmetalation with  $\text{ZnCl}_2$  to form the corresponding organozinc intermediate **40**. Subsequent Pd-catalyzed Negishi cross-coupling reaction under mild conditions provided the desired arylated fused bicycles **41** with indole, benzothiophene and benzofuran heterocyclic cores in good to excellent yields of up to 98% (Scheme 13).<sup>113</sup> Under the optimized reaction conditions, fused bicyclic heteroaromatic compounds containing different functional groups with electron-poor and electron-rich substituents were obtained, making this approach widely applicable for the synthesis of pharmaceutically active molecules (API).

Unsinn *et al.* presented an improved strategy for the synthesis of bis-heteroaryl zinc reagents **43** and reported on their subsequent reaction with various electrophiles. The refined procedure using a  $\text{TMP-Mg}$  base in the presence of  $\text{ZnCl}_2$  is



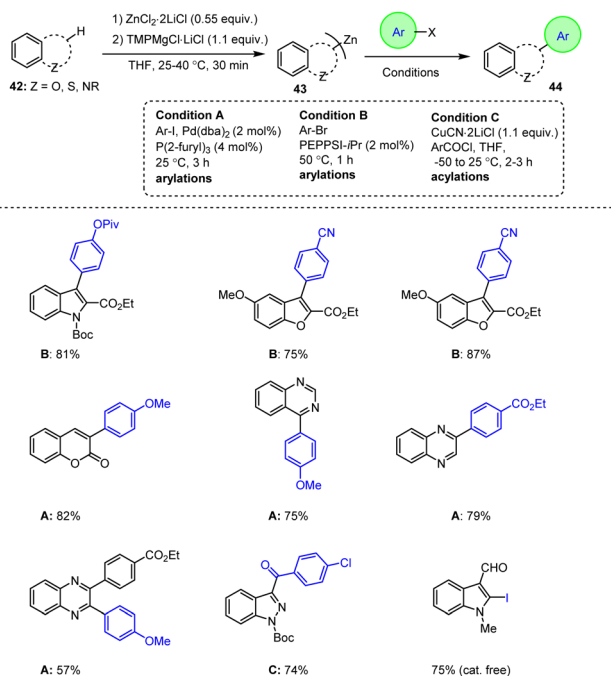
**Scheme 12** Pd-Catalyzed Negishi cross-coupling reactions of indazolyl zinc reagents.



**Scheme 13** Pd-Catalyzed benzylation of 2-methyl-5 membered fused heterocycles using  $\text{TMPLi}$  base.

preferable to the methods previously developed by Knochel *et al.* in which zinc bases are prepared from commercially available 2,2,6,6-tetramethylpiperidinyll. Most importantly, this novel protocol enables the isolation of heterocyclic products in high yields under mild conditions and with shorter reaction times. This is particularly important for the synthesis of organozinc reagents on an industrial scale and for the subsequent arylation and acylation reactions. Remarkably, the organozinc



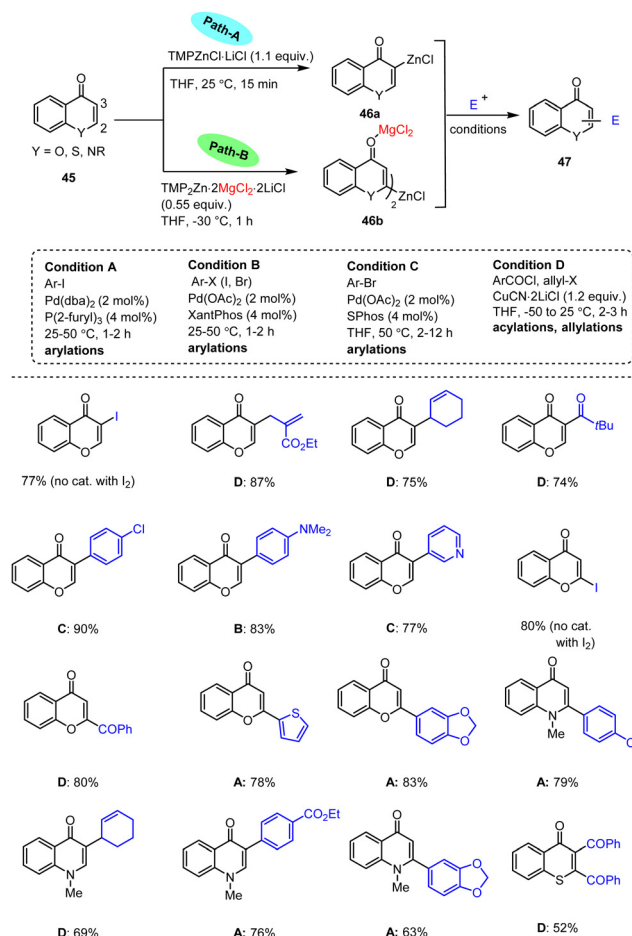


**Scheme 14** Functionalization of fused heteroaromatic indole, benzofuran, coumarin, quinoxaline and benzothiophene derivatives.

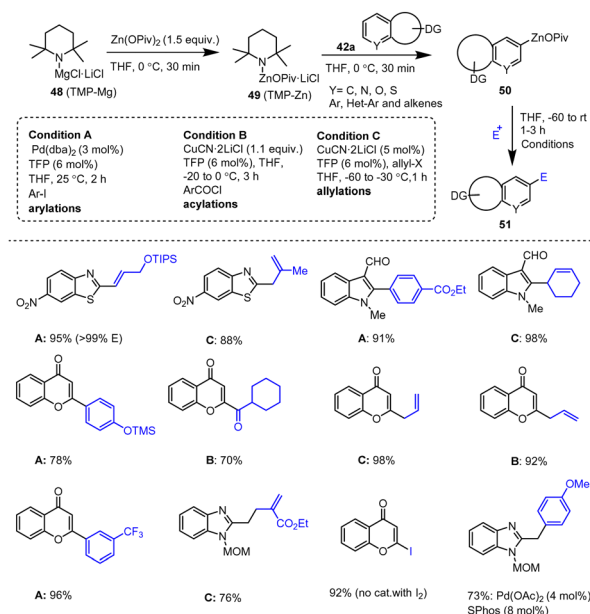
reagents not only exhibited excellent reactivity, but also tolerated a wide range of sensitive functional groups. Consequently, a direct conversion to the corresponding highly desirable organometallic zinc reagents **43** was possible, which could then be readily reacted with various electrophiles to generate functionalized heterocyclic compounds **44** in high yields (Scheme 14).<sup>114</sup>

Klier *et al.* presented a Lewis acid that triggered the regio-selective metalation of several chromones and quinolones **45**. In the absence of the Lewis acid  $\text{MgCl}_2$ , zincation is observed at the C-3 position, whereas in the presence of  $\text{MgCl}_2$ , zincation is observed at the C-2 position. Subsequent Pd-catalyzed Negishi  $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^2)$ -coupling under mild conditions afforded the corresponding desired functionalized fused 6-membered heterocycles **47** in good to excellent yields in the range of 63–90% (Scheme 15).<sup>115</sup>

Stathakis *et al.* used a wide range of interesting organozinc pivalates **50** prepared by  $\text{TMPZnOPiv}$ -mediated selective metalation methods. These organozinc reagents showed high stabilities and good reactivities in C–C cross-coupling reactions with various readily available electrophiles. In addition to CuCN-mediated acylation and allylation reactions, Pd-catalyzed Negishi couplings were performed in the presence of catalytic amounts of  $\text{Pd}(\text{dba})_2$  and the ligand TFP in THF. The resulting solid organozinc pivalates of type **50** are easy to handle in industrial experiments because their stability is maintained (>90%) for 4–6 h. As shown in Scheme 16, a broad spectrum of aryl and alkenyl zinc pivalates efficiently reacted with different electrophiles, such as aryl halides, acid chlorides, allyl bromides and iodine, leading to the production of functionalized heterocyclic compounds **51** in good to excellent yields.<sup>116</sup>

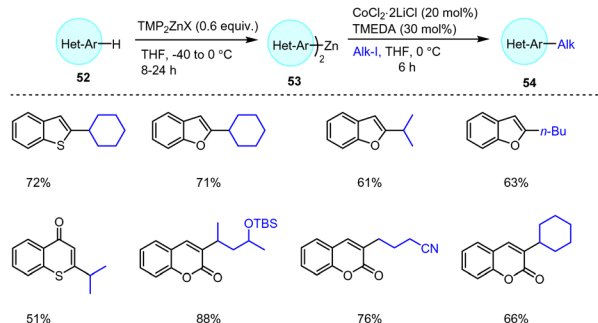


**Scheme 15** TMP-Base mediated functionalization of chromones, quinolones and thiochromones using Pd-catalysis.



**Scheme 16** Pd- and Cu-Catalyzed cross-couplings of organozinc pivalates.



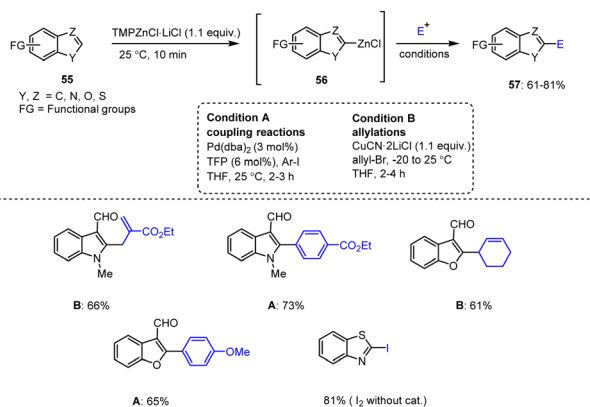


**Scheme 17** Cobalt-catalyzed cross-coupling reactions of heteroaryl zinc reagents with alkyl halides.

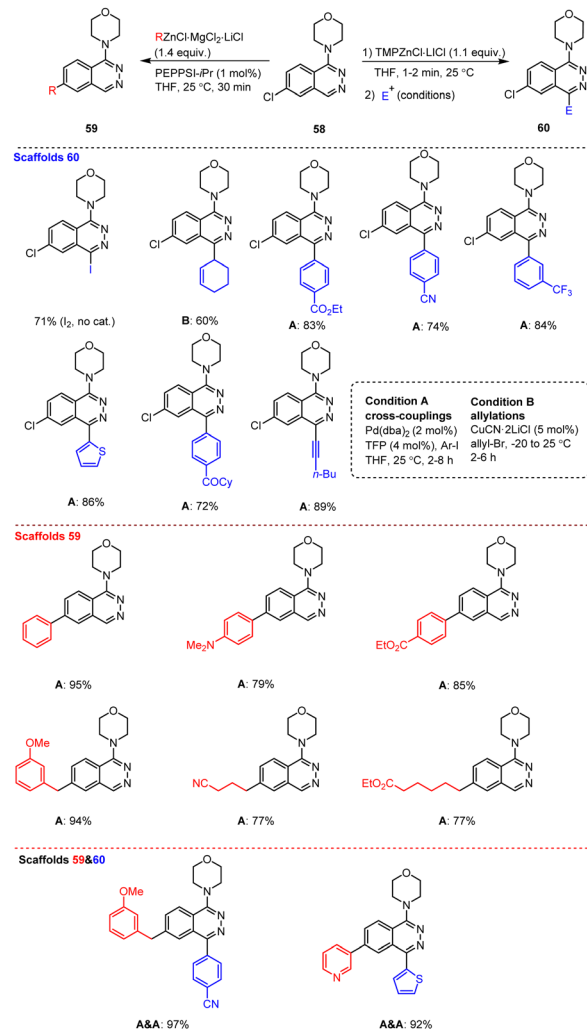
A simple and efficient cobalt-catalyzed Negishi-type cross-coupling reaction of heteroaromatic zinc reagents **53** with secondary and primary alkyl iodides or bromides using a THF-soluble homogeneous catalytic system of  $\text{CoCl}_2 \cdot 2\text{LiCl}$  (20 mol%) and TMEDA (30 mol%) allowed production of the desired alkylated heterocycles **54** in yields of up to 88%. As shown in Scheme 17, the required organozinc reagents were prepared from readily available heteroaromatic compounds **52** via a TMPZn-mediated selective metalation reaction.<sup>117</sup>

Bresser *et al.* reported a wide range of functionalized heteroaryl-zinc reagents synthesized by directed zincation of the sensitive and weakly deactivated heteroaromatic compounds **55** with TMPZnCl under distinct optimized conditions. The resulting heteroaryl-zinc organometallics **56** further exhibited excellent reactivity in various electrophilic addition reactions, and afforded the corresponding heteroaromatic compounds **57** in moderate to high yields (Scheme 18).<sup>118</sup>

Crestey *et al.* described a strategy for the functionalization of phthalazine scaffolds via regioselective zincation of chlorophthalazines using TMPZnCl·LiCl under microwave irradiation. This approach led to novel polysubstituted phthalazine derivatives of type **60** after trapping the resulting organozinc reagents with various electrophiles. In addition, Negishi cross-coupling reactions between chlorophthalazines and organometallic reagents were conducted using a Pd catalyst, providing



**Scheme 18** Regio- and chemo-selective zincation of fused heteroaromatics using TMPZnCl.



**Scheme 19** Synthesis of polyfunctionalized phthalazines using TMPZnCl·LiCl.

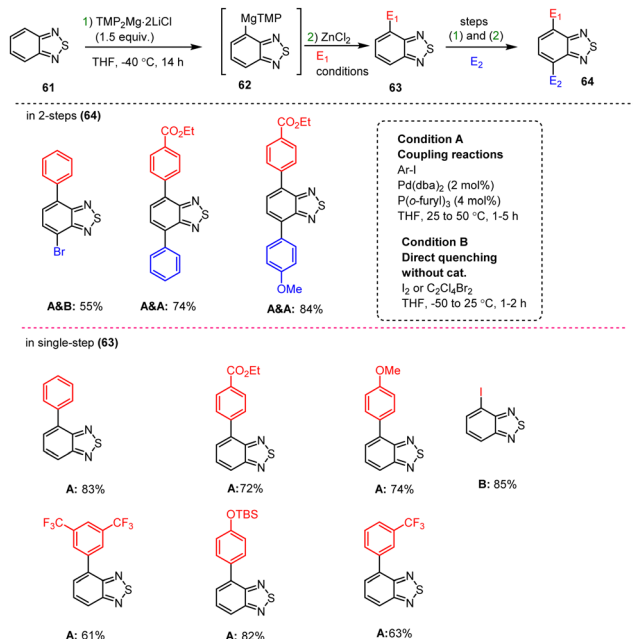
highly functionalized phthalazine scaffolds **59** in excellent yields of up to 94% (Scheme 19).<sup>119</sup>

Zimdars *et al.* demonstrated the selective metalation of positions 4 and 7 of the benzo[*c*][1,2,5]thiadiazole scaffold **61** using TMP-bases in THF at  $-40\text{ }^{\circ}\text{C}$  for 14 h. The corresponding reactive Mg-intermediate **62** was readily transmetalated with  $\text{ZnCl}_2$  followed by electrophilic quenching. In this way, Pd catalysis enabled the preparation of functionalized asymmetric disubstituted benzothiadiazole derivatives **64** in high yields, as shown in Scheme 20.<sup>120</sup>

In 2020, Balkenhohl *et al.* reported a powerful model for predicting site-selective metalation approaches with TMPZnCl·LiCl. The  $\text{pK}_\text{a}$  values of the functionalized condensed N-heterocycles were calculated and compared with experimental results of deprotonations. Thus, the fused heteroaromatic bicycles **65** such as pyrido[2,3-*b*]pyrazine, imidazo[1,2-*b*]pyridazine, [1,2,4]triazolo[4,3-*a*]pyrazine, [1,2,4]triazolo[1,5-*a*]pyrimidine, and imidazo[1,5-*a*]pyridine as well as quinazoline were smoothly deprotonated at the predicted positions ( $\text{pK}_\text{a} = 24.6\text{--}39.7$ ), leading to the corresponding aryl zinc reagents **66** in 40–70% yield. After iodolysis or palladium-catalyzed Negishi



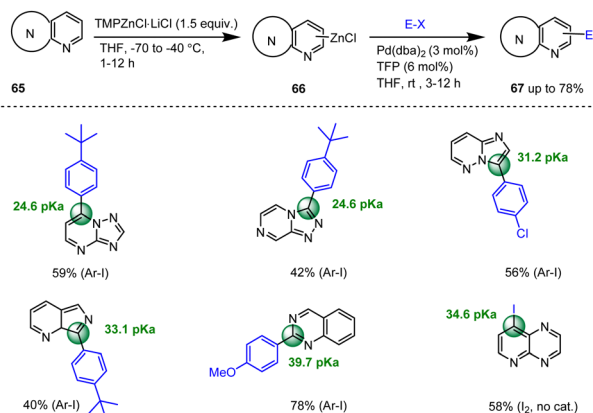




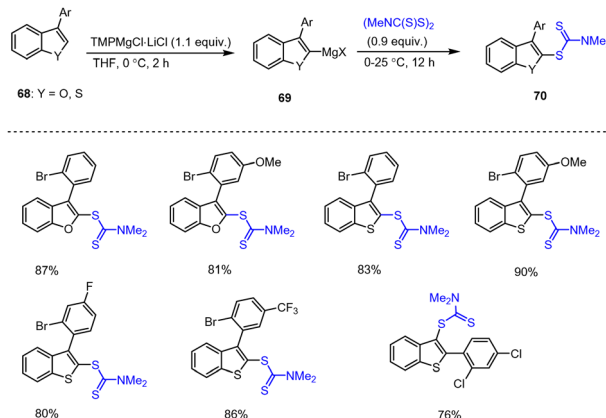
**Scheme 20** Double functionalization of benzo[c][1,2,5]thiadiazole via TMPMg-mediated coupling reactions.

cross-coupling reactions, the expected highly functionalized N-heterocycles of type **67** were obtained in 42–59% yields (Scheme 21).<sup>121</sup>

Regioselective magnesiation of benzothiophene and benzofuran scaffolds **68** with TMPMgCl·LiCl in THF at 0 °C for 2 h, followed by a 12 h trapping reaction using the thio-electrophile (Me<sub>2</sub>NC(S)S)<sub>2</sub> afforded the desired benzothienyl dithiocarbamates **70** in excellent yields of 76–90%. Kienle *et al.* also prepared substituted 2-aryl and 3-aryl benzothiophene derivatives under similar reaction conditions (Scheme 22).<sup>122</sup> This method allows polycyclic heteroaromatic compounds such as dibenzothiophenes and dibenzothiopheneothiophenes scaffolds to be prepared in good yields. Derivatives of benzothiophenes, dibenzothiophenes, dibenzothiopheno-thiophenes and their S-heterocyclic congeners are broadly applied in various fields



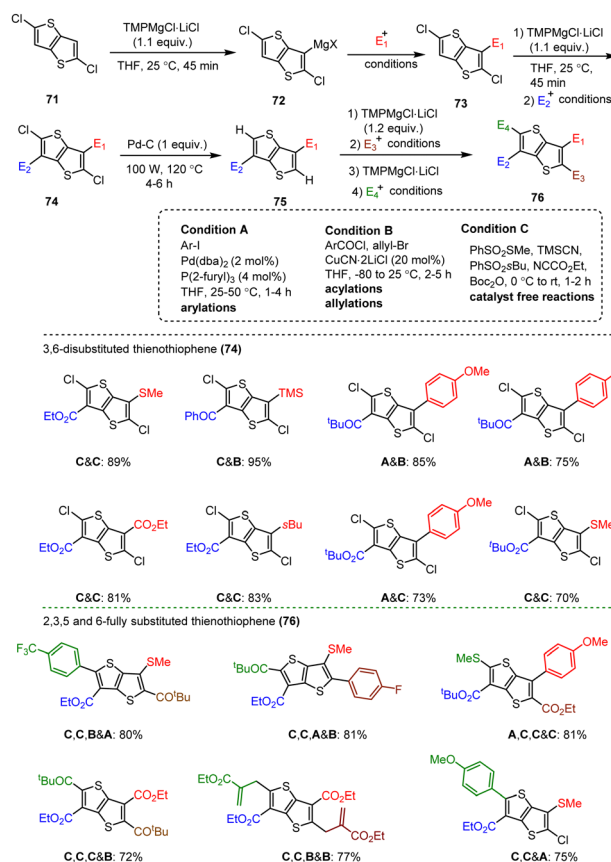
**Scheme 21** TMPZNCl-LiCl-promoted regioselective deprotonations and subsequent functionalizations of N-heterocycles.



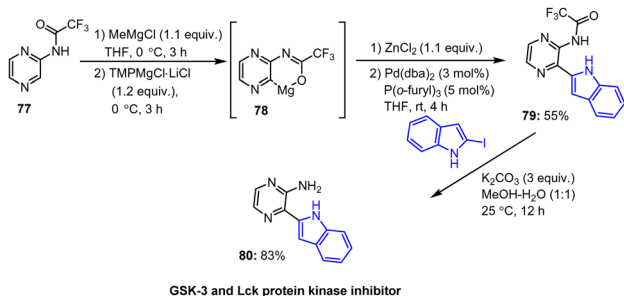
**Scheme 22** Preparation of heteroaryl dithiocarbamates using TMPMgCl·LiCl for metalation.

such as in agriculture, for pharmaceuticals and dyes, as well as in building blocks for conductive polymers.

Kunz *et al.* showed that direct magnesiation with TMPMgCl·LiCl enables highly regioselective and complete functionalization of the thieno[3,2-*b*]thiophene core **71** under mild conditions. A wide variety of sensitive functional groups can be successfully introduced as substituents, yielding various polyfunctionalized fused thienothiophenes **74** and **76** (Scheme 23),<sup>123</sup> which are otherwise difficult to process into



**Scheme 23** Synthesis of 2,3,5 and 6-substituted thienothiophenes.



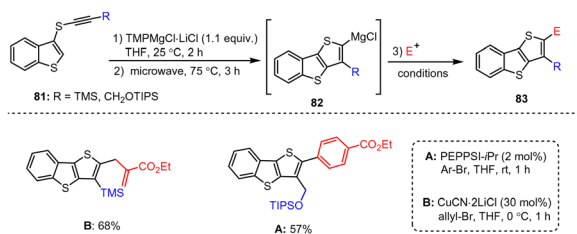
**Scheme 24** Synthesis of GSK-3 and Lck protein kinase inhibitor via chemoselective magnesiation, followed by Pd-catalyzed coupling reaction and deprotection.

promising heterocyclic scaffolds. This protocol could allow the fine-tuning of material properties of such S-heterocycles (*e.g.* absorption bands, overlap of frontier orbitals) by introducing specific side chains into monomeric building blocks. The conjugated heterocyclic aromatic compounds represent a new class of S-containing condensed bicyclic heterocycles and their polymers, which may also be of interest as materials for OLEDs or solar cells.

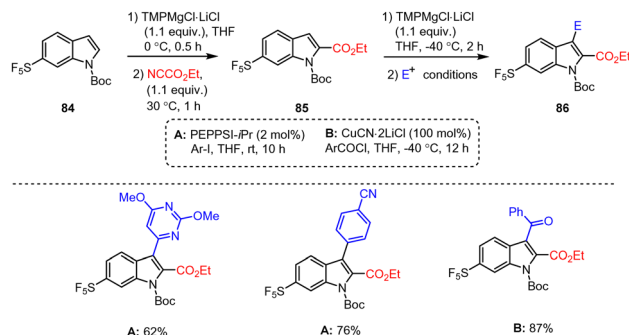
Knochel and co-workers developed a practical magnesiation protocol for trifluoromethylated pyrazinamide **77**, which is carried out at 0 °C and is compatible with carbonyl functionalities. Subsequent quenching with heteroaryl halides led to satisfactory yields of arylated indole **79**. After deprotection of the pyrazinamide with  $K_2CO_3$  under green conditions, the targeted free heterocyclic amine **80** was obtained in good yield (Scheme 24).<sup>124</sup>

Starting from alkynyl(aryl)thioethers **81**, Kunz *et al.* developed a novel intramolecular carbomagnesiation protocol for the synthesis of magnesiated benzothiophene intermediate **82**. Other heteroaromatic Mg species also reacted with readily accessible electrophiles to give the highly functionalized benzo[*b*]thieno[2,3-*d*]thiophenes of type **83** in excellent yields (Scheme 25).<sup>125</sup> The method tolerates a wide range of functional groups, and the authors further elaborated the cyclization process to produce highly diverse condensed benzothiophene scaffolds as well as new complex heterocyclic analogs under mild conditions.

Frischmuth *et al.* prepared a wide range of polyfunctional  $SF_5$ -substituted indole analogs **86** using  $TMPMgCl-LiCl$ . This was accomplished *via* the formation of organomagnesium intermediate **85** through the reaction between indole **84** and



**Scheme 25** Functionalized benzo[*b*]thiophenes obtained by magnesiation and subsequent quenching with electrophiles.



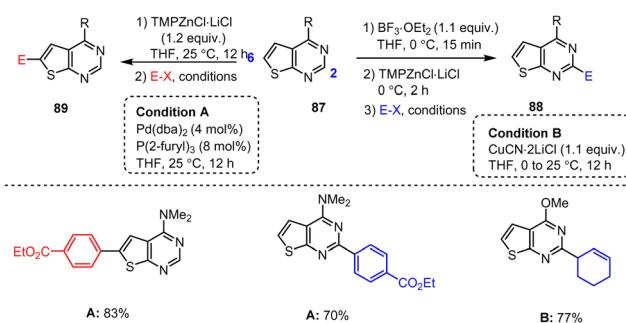
**Scheme 26** Functionalization at the position C-2 and C-3 of protected  $SF_5$ -substituted indole derivative using  $TMPMgCl-LiCl$ .

the TMP base over a period of 0.5–2 h at moderate conditions (Scheme 26).<sup>126</sup> A library of  $SF_5$ -substituted heteroaromatic compounds could be accessed with the help of this organometallic strategy to enable the discovery of new biologically active indole compounds.

Groll *et al.* showed that the combination of  $BF_3 \cdot OEt_2$  with  $TMPZn$  bases enables regioselective functionalization of fused heterocycles and thieno-pyrimidines. Remarkably, the use of  $BF_3 \cdot OEt_2$  together with  $TMPZn$  bases enabled efficient zincation of the C-2 position, whereas metalation at the C-6 position was observed in the absence of the Lewis acid. The pre-formed organozinc species subsequently reacted with different electrophiles smoothly to produce the desired functionalized heterocycles **88** and **89** in good yields (Scheme 27).<sup>127</sup>

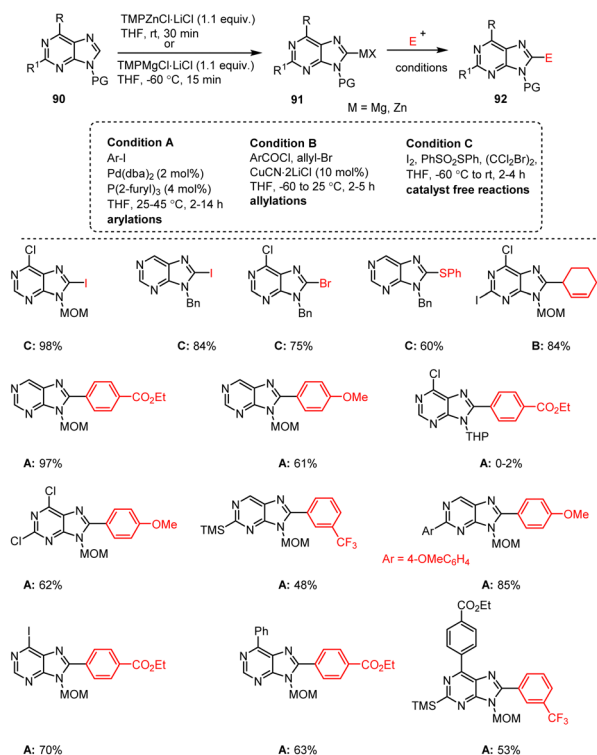
The regioselective functionalization of a broad spectrum of N-protected purine scaffolds was successfully performed by Crestey *et al.* For this purpose, they applied a TMP base to substituted purine derivatives **90** for forming a zinc or magnesium intermediate **91**. This is furnished after trapping with various electrophiles such as  $I_2$ ,  $Br_2$ , Ar-I, and allyl bromide the desired highly substituted purine analogs **92** (Scheme 28). Subsequent arylation reaction was achieved with  $Pd(dba)_2$  (2 mol%) in combination with the ligand TFP (4 mol%) at 45 °C for 14 h, while for the corresponding allylation reaction  $CuCN \cdot 2LiCl$  (10 mol%) in THF at –60 to 25 °C for 2 h was used.<sup>128</sup>

Klatt *et al.* reported a new and efficient protocol for the regioselective metalation of the condensed heteroaromatic cinnoline backbone using two complementary methods. While



**Scheme 27** Switchable, regioselective metalation of thieno-pyrimidines with  $TMPZn$ -base.



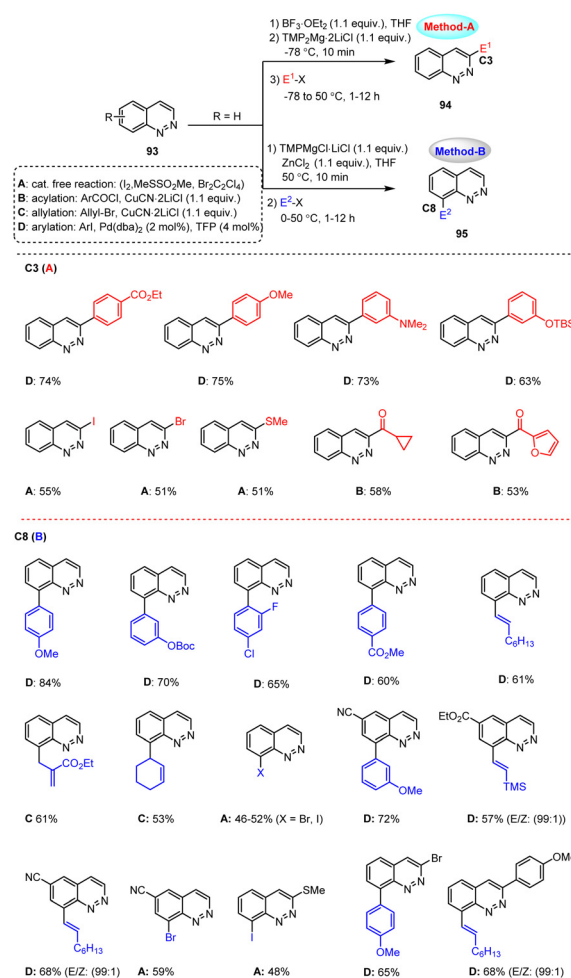


**Scheme 28** Regioselective functionalization of purine scaffolds with TMP metal bases.

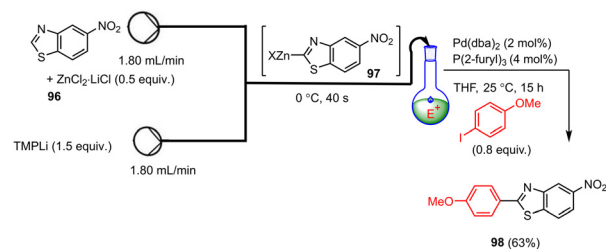
the use of  $\text{BF}_3\cdot\text{OEt}_2$  and  $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$  (method A) allowed magnesiation at the C-3 position, application of  $\text{TMPMgCl}\cdot\text{LiCl}$  (method B) enabled selective zincation at the C-8 position of the cinnoline skeleton. By using the TMP-Mg base, this reaction allowed the formation of reactive Mg intermediates of both simple and substituted cinnoline derivatives. Subsequent coupling reactions with various electrophiles such as  $\text{X}_2$ , aryl halides, allyl bromide and acid chlorides in the presence of  $\text{Pd}(\text{dba})_2$  (2 mol%) with TFP (4 mol%) or  $\text{CuCN}\cdot 2\text{LiCl}$  (1.1 equiv.) furnished the desired polyfunctionalized heterocycles **94** and **95** in good to excellent yields (Scheme 29).<sup>129</sup>

By using a flow process, highly sensitive, electron-poor benzothiazoles **96** can be efficiently transmetalated upon treatment with  $\text{TMPLi}$  in the presence of  $\text{MgCl}_2$  or  $\text{ZnCl}_2\cdot 2\text{LiCl}$  to yield the corresponding organomagnesium or organozinc reagents such as **97** (Scheme 30). According to Becker *et al.*,<sup>130</sup> these flow reactions take place under significantly milder conditions than in the batch process within 40 s (0 °C instead of  $-78$  °C). The resulting heteroaromatic metalation intermediates can then be reacted with various electrophiles, whereby the reaction scope of the flow metalations is also significantly larger than in the corresponding batch processes. In addition, these flow reactions can be easily scaled up by extending the reaction time without further optimization steps. As a result, easily modified benzothiazole scaffolds such as **98** can be produced in high yields.

An efficient method for the functionalization of substituted quinoxalines by metalation at the C-6 and C-8 positions was



**Scheme 29** Regioselective metalations for subsequent functionalization of the cinnoline scaffold.



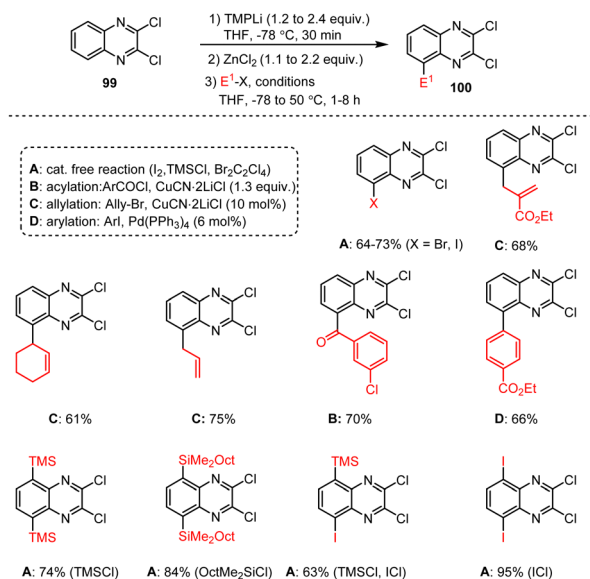
**Scheme 30** Continuous-flow zincation of benzothiazole followed by Pd-catalyzed trapping with Ar-I.

developed by Nafe *et al.* using  $\text{TMPLi}$  and 2,3-dichloroquinoxalines. This protocol enables the synthesis of interesting, highly functionalized quinoxaline scaffolds *via* subsequent Pd-catalyzed cross-couplings (Scheme 31).<sup>131</sup>

In addition, the resulting functionalized products can be used further to construct expanded O- or S-heterocyclic compounds *via* annellation reactions. Such expanded quinoxaline scaffolds are characterized by robust photoluminescence with high molecular extinction coefficients within the blue and





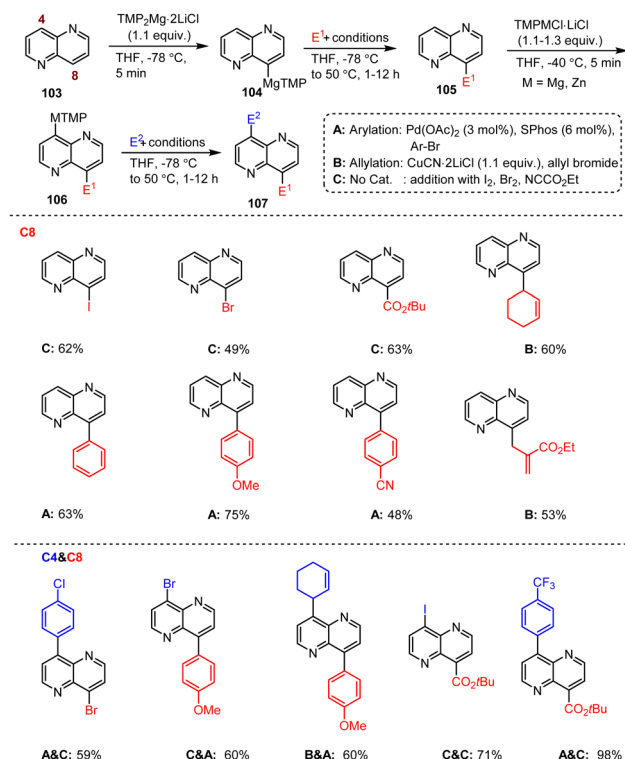


**Scheme 31** Synthesis of substituted quinoxalines using TMPLi, ZnCl<sub>2</sub>, and electrophiles.

green spectral range and thus represent interesting potential fluorescent imaging tools with fine-tuned optical properties (Scheme 32).<sup>132</sup>

Balkenhohl *et al.* developed regioselective metalation and functionalization reactions of the condensed 1,5-naphthyridine scaffold **103** mediated by TMP-metal bases. A clever combination of TMPMg and TMPZn bases allowed regioselective bisfunctionalization of the 1,5-naphthyridine core, which is an important heteroaromatic scaffold. Furthermore, the C-8 substituted 1,5-naphthyridine **105** allows additional regioselective functionalization at the C-4 position by using TMPMg or TMPZn bases under mild conditions (Scheme 33).<sup>133</sup> Thus, this reaction method is not only a key technique for the design and synthesis of OLED materials, but can also be used for pharmaceutical applications, such as the production of potentially antibacterial and antiviral agents.

A recent discovery of a highly regioselective functionalization of pyrazolo[1,5-*a*]pyridine by TMPMgCl·LiCl at the C-2 and

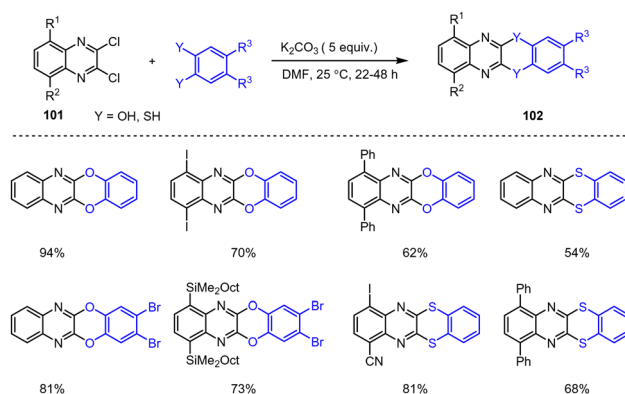


**Scheme 33** Regioselective metalation and functionalization of 1,5-naphthyridines.

C-7 positions, guided solely by the presence or absence of BF<sub>3</sub>·OEt<sub>2</sub>, was also described by Balkenhohl *et al.* A wide range of functionalized pyrazolo[1,5-*a*]pyridine derivatives **109** and **110** thus obtained under moderate metalation conditions with suitable regioselectivities. The organomagnesium reagents prepared *in situ* reacted smoothly with various electrophiles, such as I<sub>2</sub>, C<sub>2</sub>Cl<sub>4</sub>Br<sub>2</sub>, NCCO<sub>2</sub>Et, MeSSO<sub>2</sub>Me, and Tietze's reagent. Moreover, CuCN-mediated acylation and allylation reactions were also successfully carried out (Scheme 34).<sup>134</sup>

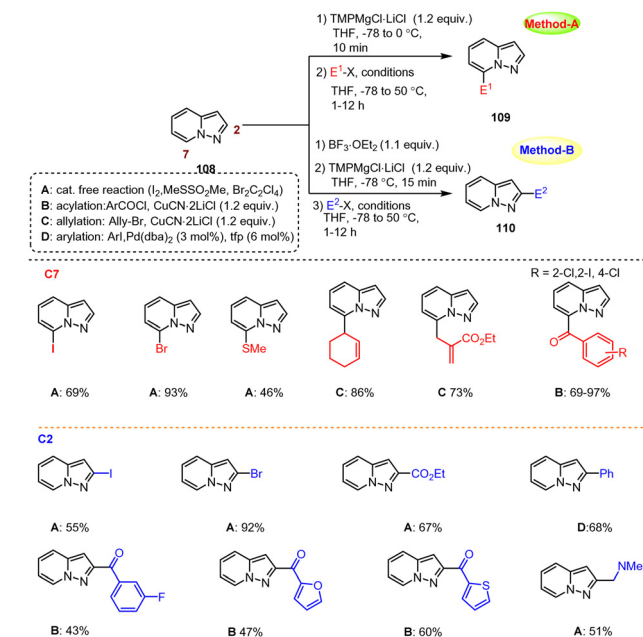
Knochel, Wagschal *et al.* reported a highly regioselective metalation of various aryl-substituted azoles by using a sterically hindered TMPMgBu base. In this reaction, arylazole **111** for example, was allowed to react with TMPMgBu in a toluene/hexane combination at room temperature for 1–6 h before it was subjected to Negishi cross-coupling reactions with various (hetero)aryl halides in the presence of organozinc reagents and a suitable palladium catalyst. The resulting polyfunctionalized arylazole scaffolds **112** were isolated in excellent yields of up to 91% (Scheme 35).<sup>135,136</sup> This protocol could be useful for preparing key intermediates of active pharmaceutical ingredients (API), as well as for several late-stage modifications of drug-related aromatic compounds. Mechanistic studies emphasize the key role of the TMPMg base for the observed selectivity, which could be exploited for different cross-coupling reactions and synthetic applications in organic chemistry.

Furthermore, Knochel, Bein and co-workers reported a selective functionalization sequence of readily available 7-substituted SEM-protected 1*H*-imidazo[1,2-*b*]pyrazole scaffold.



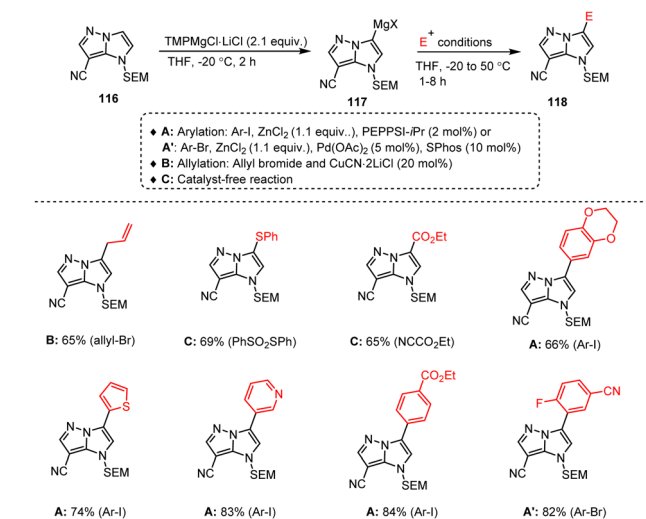
**Scheme 32** Functionalization of quinoxalines at C-2 and C-3 for annulation reactions.





**Scheme 34** Metalation of pyrazolo[1,5-*a*]pyridine for functionalization at C-2 and C-7.

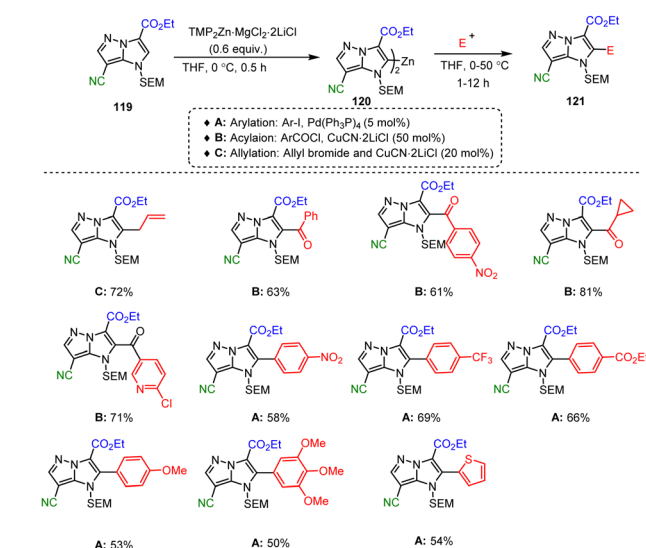
Successive functional group installations in the 3- and 2-positions were achieved through consecutive metalations using metal amides followed by quenching reactions with suitable electrophiles. For example, the cyano-substituted 1*H*-imidazo[1,2-*b*]pyrazole **116** was selectively metalated at C-3 with



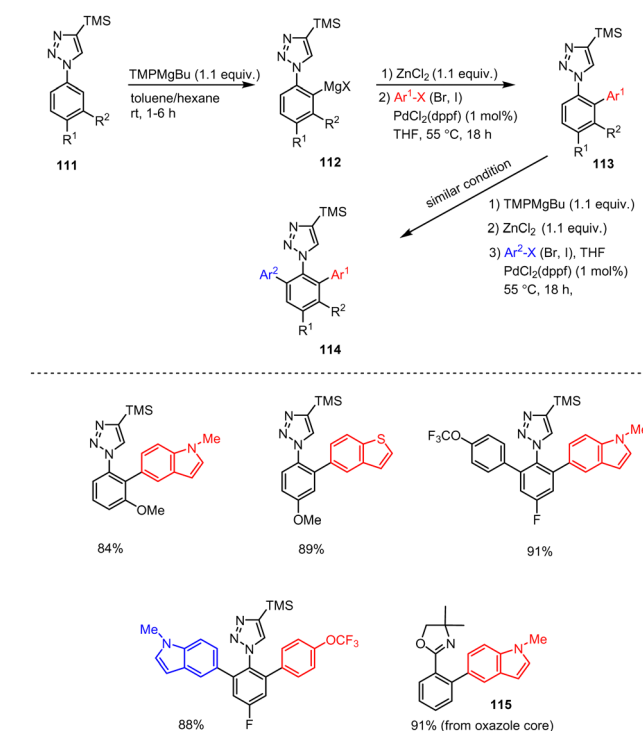
**Scheme 36** Selective metalation and quenching reactions of 7-CN substituted 1*H*-imidazo[1,2-*b*]pyrazole derivatives.

TMPMgCl-LiCl to generate the magnesiated intermediate **117**, which was then successfully reacted with different electrophiles to provide *e.g.*, allylated, acylated, thiolated as well as Negishi-type arylation products **118** in 65–84% yields (Scheme 36).<sup>137</sup>

Further functionalization in position 2 of the 3-ester substituted *N*-heterocycle **119** was achieved *via* a bis-organozinc species **120** generated upon treatment with bis-base TMP<sub>2</sub>Zn·MgCl<sub>2</sub>·2LiCl at 0 °C in THF. Subsequent Cu-catalyzed acylations with various types of acylchlorides and Negishi-type cross-couplings proceeded smoothly to afford the desired trisubstituted heterocycles **121** in good yields (Scheme 37).<sup>137</sup> The high chemoselectivity of the reactive intermediate zinc species even allowed the use of electrophiles containing sensitive functional groups such as an ester or a nitro group.

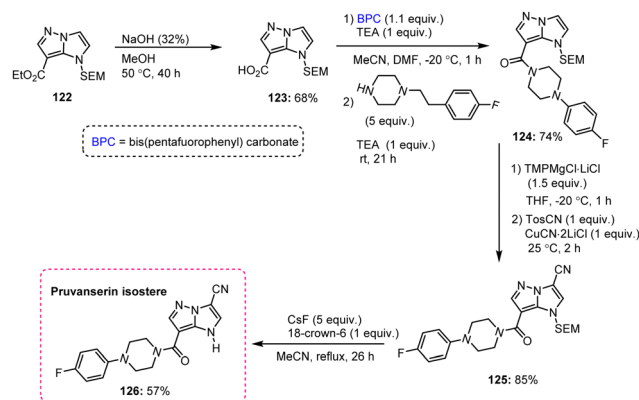


**Scheme 37** Selective metalation and functionalization of the 7-CN and 3-CO<sub>2</sub>Et disubstituted 1*H*-imidazo[1,2-*b*]pyrazoles.



**Scheme 35** Regioselective metalation and functionalization of various aryl substituted azole systems using a sterically hindered TMPMgBu base.

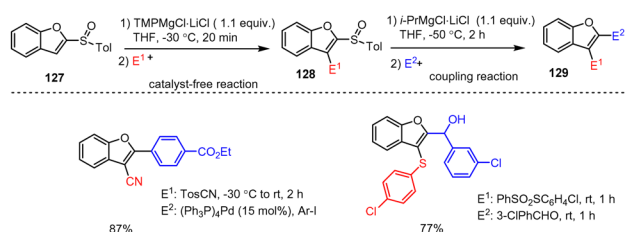




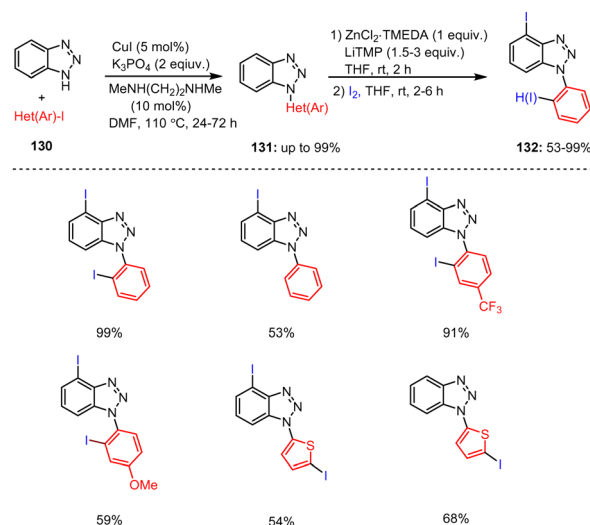
**Scheme 38** Consecutive functionalization of 1*H*-imidazo[1,2-*b*]pyrazole within the synthesis of the pruvanserin isostere **126**.

Moreover, this consecutive functionalization sequence was applied to the synthesis of a non-classical isostere **126** of the indolyl drug pruvanserin (Scheme 38). The latter is a selective 5-HT<sub>2A</sub> serotonin receptor antagonist suffering from low solubility under physiological conditions. Comparative assays between the original drug and the isostere revealed a significantly improved solubility in aqueous media due to the substitution of the indole ring with the 1*H*-imidazo[1,2-*b*]pyrazole core. Fused five-membered N-heterocyclic scaffolds such as 1*H*-imidazo[1,2-*b*]pyrazoles recently attracted much attention as key structural elements for many pharmaceutical, agrochemical and material science applications.<sup>138</sup>

Melzig *et al.* established an efficient two-step protocol for the 2,3-difunctionalization of benzofuran scaffolds **127** (Scheme 39). Here in the first step, a sulfoxide group acts as a metalation-directing group (DoM) in the presence of TMPMgCl·LiCl to allow smooth *ortho*-magnesiation and electrophile trapping. In the second step, the sulfoxide group of **128** works instead as a leaving group enabling a sulfoxide-magnesium exchange in the presence of commercially available Turbo-Grignard (*i*-PrMgCl·LiCl). Upon further reaction of the *in situ* prepared novel organomagnesium species with electrophiles, highly functionalized heterocyclic compounds **129** were obtained in good yields. The chemoselective TMPMgCl·LiCl and *i*-PrMgCl·LiCl reagents are compatible with a wide range of functional groups (*e.g.* F, Cl, CF<sub>3</sub>, CN, CO<sub>2</sub><sup>t</sup>Bu, alkynyl, ether, thioether), so that this method is particularly suitable for gram-scale syntheses in standard laboratories.<sup>139</sup>



**Scheme 39** TMPMgCl-Mediated metalation of benzofuran followed by a sulfoxide–Mg exchange reaction and trapping with various electrophiles.



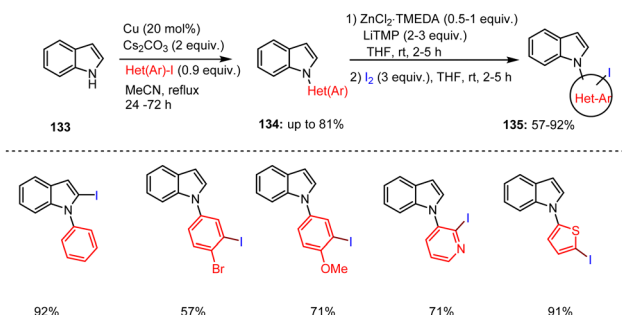
**Scheme 40** Deproto-metalation of benzotriazole by TMP-base for subsequent iodination.

Mongin, Halauko, Chevallier and co-workers developed a deproto-metalation method for several *N*-arylated 1*H*-benzotriazoles **130** with TMP-bases. The *in situ* prepared organometallic reagents reacted readily with commercially available iodine reagents and gave mono- or diiodinated heterocyclic compounds **132** in good to high yields. Varying amounts of the TMP-base (1.5–3 equiv.) were used with substrates bearing electron-rich and electron-poor substituents (Scheme 40).<sup>140</sup>

The same group also succeeded in functionalizing indole derivatives **134** under very similar conditions, *i.e.*, in the presence of TMPLi and ZnCl<sub>2</sub>·TMEDA. For example, selective deproto-metalation of the protected indoles followed by quenching with I<sub>2</sub> led to the formation of the iodinated indole derivatives **135** in satisfactory yields (Scheme 41).<sup>141</sup>

In addition, a strategy for the direct metalation of methylated quinoline and quinoxaline scaffolds **136** using LDA and TMPLi as bases was reported in 2023. Subsequent capture reactions with various electrophiles at low temperatures led to quinolinyl alcohol and amine derivatives **137** in moderate yields (Scheme 42).<sup>142</sup>

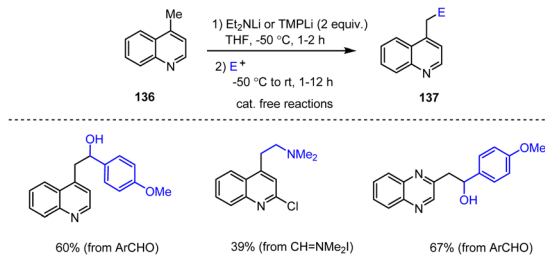
Clososki *et al.* described the straightforward C-2 and C-5 functionalization of indolizine motifs **138** with an ester group



**Scheme 41** Deproto-metalation of protected indole by TMP-base for iodination.

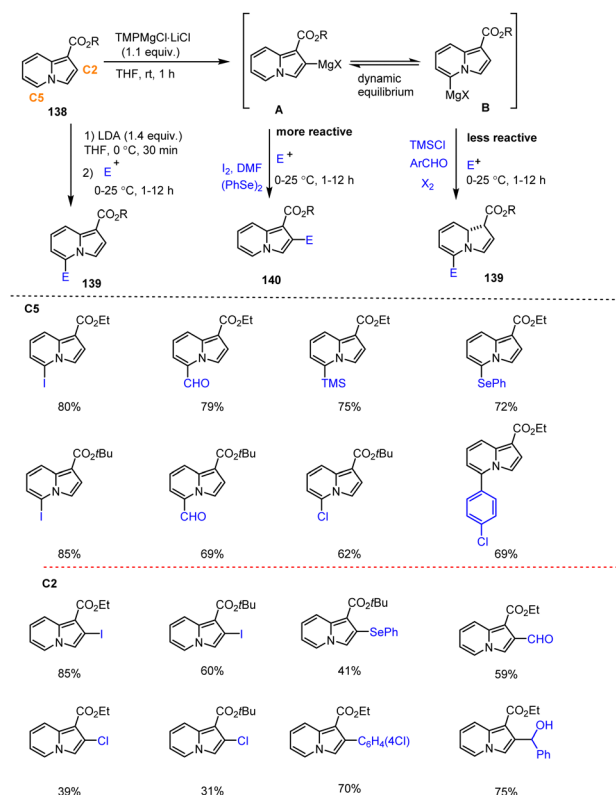






**Scheme 42** Deproteo-metalation of methylated quinolines and quinoxalines using LDA or TMPLi bases for subsequent electrophilic trapping reactions.

at C-1. The directed metalation process took place under mild conditions using the organometallic bases LDA or TMPMgCl·LiCl, whereby the reaction of the corresponding organometallic intermediates (A and B) with different electrophiles enabled the production of difunctionalized indolizines **139** and **140** in high yields. While LDA favoured C-5 functionalization, the TMPMg base yielded mostly C-2 functionalized derivatives *via* selective *ortho*-metalation. However, the regioselectivity of these reactions was not only dependent on the choice of the base. Rather, in the case of the TMPMgCl·LiCl-mediated reaction, electrophile-controlled regioselectivity was observed due to a dynamic equilibrium between the two reactive C-2/C-5-organomagnesium species. The scope of applicable substrates for this process is summarized in Scheme 43<sup>143</sup> affording a



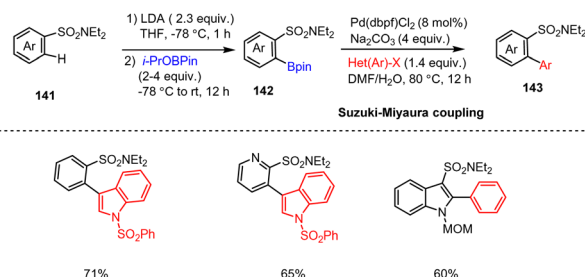
**Scheme 43** LDA- and TMPMgCl-mediated selective directed metalation of indolizine derivatives followed by reaction with various electrophiles.

wide range of potentially biologically active heterocyclic compounds in good yields and with high functional group tolerance.

### 3 Functionalization of fused bicyclic heteroaromatics with organolithium reagents RLi

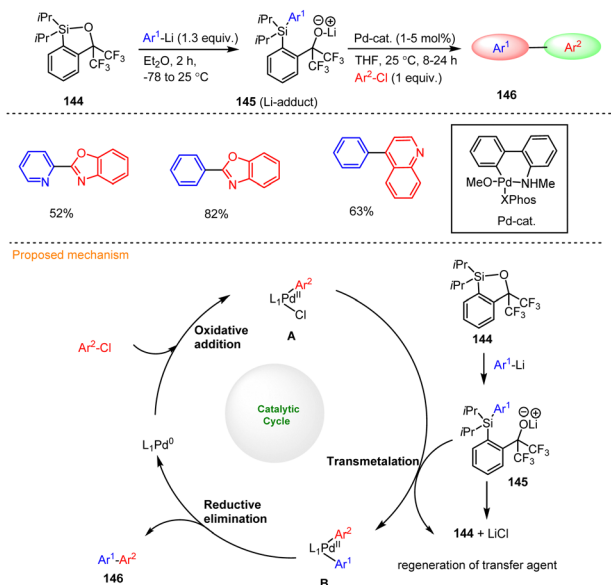
Snieckus and co-workers presented a general method for preparing air-stable *ortho*-boropinacolato aryl sulfonamides **142** *via* the directed *ortho*-metalation (DoM) method. Metalation of aryl sulfonamides of type **141** with LDA at  $-78^{\circ}\text{C}$  generates highly reactive aryl-lithium species. Subsequent trapping with *i*-PrOBPin boron reagents (4 equiv.) produced the corresponding *ortho*-boropinacolato aryl(heteroaryl) sulfonamides **142** in good yields. Moreover, **142** was subjected to a Pd-catalyzed C(sp<sup>2</sup>)-C(sp<sup>2</sup>) Suzuki-Miyaura cross-coupling reaction with readily accessible aryl and heteroaryl halides in DMF/H<sub>2</sub>O at  $80^{\circ}\text{C}$  providing biaryl and heterobiaryl sulfonamides and in particular functionalized indole scaffolds **143** (Scheme 44).<sup>144</sup> This method overcomes previous failings in the preparation of aryl sulfonamide boronic acids and should be of value for medicinal chemistry programs centered on the sulfonamide functional group.

Recently, Houk, Smith and co-workers developed an efficient protocol for the palladium-catalyzed cross-coupling reaction of readily available aryl and pyridyllithium reagents **145** at room temperature using a reusable siloxane transfer reagent **144**. The crystalline, bench-stable siloxane reagent is easily prepared in a one-step protocol, and its use eliminates the need for pre-functionalization, as well as isolation of organometallic cross-coupling partners. Importantly, this reagent can be recovered and reused without sacrificing reactivity. Both electron-rich and electron-poor substrates can be efficiently cross-coupled, and a variety of common functional groups on the electrophilic partner were well tolerated (*i.e.* esters, nitriles, azaheterocycles, fluorinated aromatics and quinolines) as well as sterically burdened aryl chlorides. Hence, functionalized quinoline and benzoxazole derivatives **146** can be obtained in acceptable yields by C(sp<sup>2</sup>)-C(sp<sup>2</sup>) cross-coupling reactions of aryl lithium and aryl chlorides in the presence of Pd pre-catalyst (1–5 mol%) and the XPhos ligand (Scheme 45).<sup>145</sup> The



**Scheme 44** LDA-Mediated one-pot directed *ortho*-metalation of aryl sulfonamides followed by Suzuki Miyaura cross-couplings.



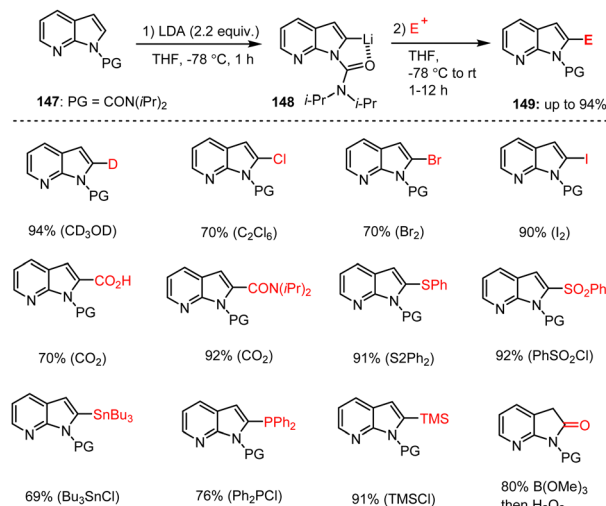


**Scheme 45** Pd-Catalyzed cross-coupling reactions of heteroaryl chlorides with aryl lithium reagents in the presence of siloxane transfer reagent **144**.

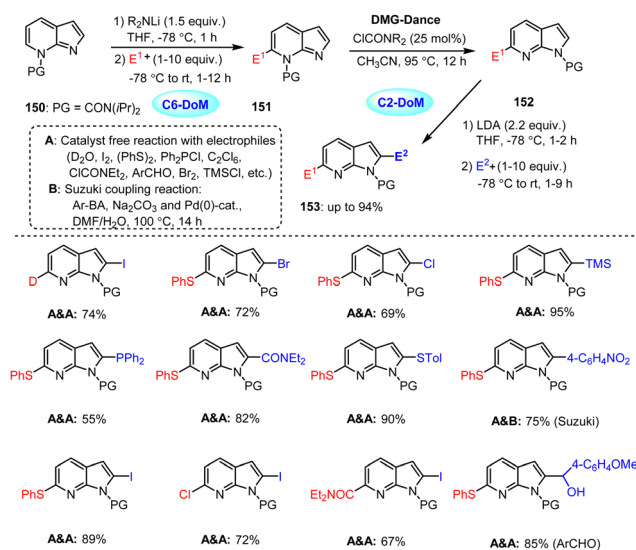
Pd-catalyzed cross-coupling reaction of the heteroaryl chlorides with aryllithium reagents comprises the following typical steps: oxidative addition to the intermediate **A**, followed by transmetalation with ArLi to form intermediate **B**. Reductive elimination finally yields the desired heterocyclic product **146** in good yield and regenerates the active Pd catalyst for the next cycle run.

Efficient regioselective functionalization of fused 7-azaindole heterocycles using LDA and amide bases was reported by Kitching, Snieckus and co-workers. Carbamoyl-protected 7-azaindole **147** underwent a rapid LDA-mediated regioselective metalation followed by trapping with various electrophiles to generate C-2-substituted 7-azaindole derivatives **149** in excellent yields (Scheme 46).<sup>146</sup>

Under similar mild conditions, the regioselective functionalization of 7-azaindole by controlled ring isomerization using directed metalation group (DMG) migration was also achieved (Scheme 47).<sup>147</sup> By using a TMPLi base, azaindole **150** was first regioselectively metalated at the C-6 position and then quenched with an electrophile to obtain a C-6-substituted derivative **151**. Subsequently, a carbamoyl group shift (a dance from N7 to N1) was performed in the presence of a catalytic amount of ClCONR<sub>2</sub>, leading to the formation of product **152**. A second directed metalation and electrophile quench sequence then provided 2,6-substituted azaindoles **153**. Overall, the controlled migration of the carbamoyl group enables multiple functionalization events of the bioactive azaindole scaffold, bypassing the removal and introduction of another DMG and instead allowing the same DMG group to direct functionalization at a new, distant site. Furthermore, the use of the directed metalation group dance strategy could be applied to a late-stage deuteration of an antipsychotic compound (L-745870)



**Scheme 46** Regioselective functionalization of Carbamoyl-protected 7-azaindoles using LDA.

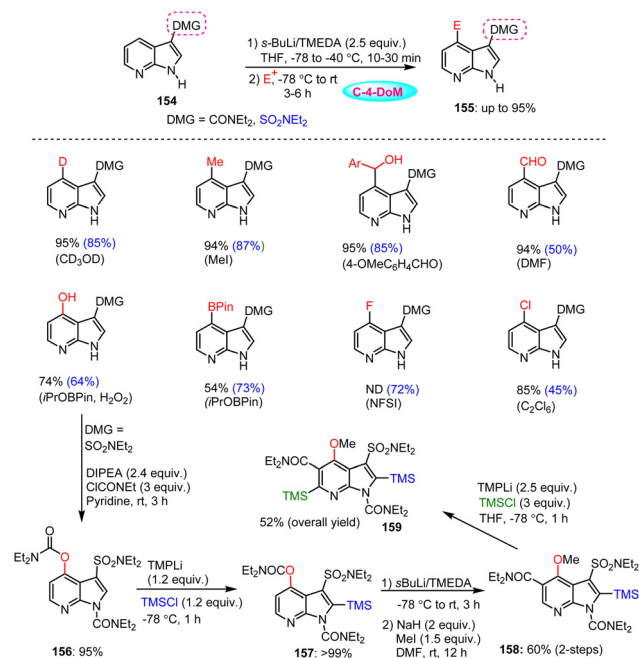


**Scheme 47** Regioselective functionalization of 7-azaindole at C-6 and C-2 positions via controlled DMG migration.

demonstrating a new strategy for the functionalization of the bioactive azaindole scaffold and related N-heterocycles.

The same research group also reported a method for a rather unusual C-4 *peri*-metalation of NH-free azaindoles **154**, in which CONET<sub>2</sub> and SO<sub>2</sub>NET<sub>2</sub> groups as DMG on C-3 allowed the highly regioselective synthesis of 4-substituted derivatives *via* anionic shielding of C-2. The reaction is robust and scalable. If such anionically shielding DMG is introduced at C-4 (**156**), successive *ortho*-metalations (DoM) of C-2 (**157**) and C-5 (**158**) are possible. The multiple, sequential DoM reactions (*i.e.*, ring-walk metalation sequences) provide a rational and generally regioselective route to polysubstituted 7-azaindoles **159** and other heterocycles of potential pharmaceutical significance (Scheme 48).<sup>148</sup>



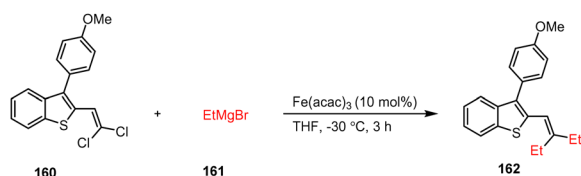


Scheme 48 Organolithium-mediated C-4-*peri*-metalation of substituted 7-azaindole derivatives followed by electrophilic additions.

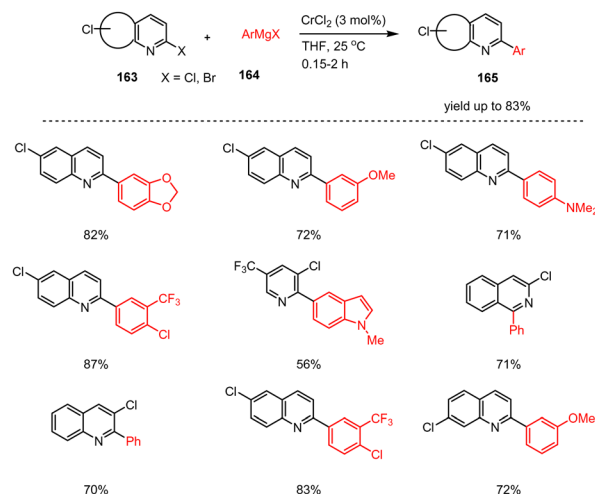
## 4 Functionalization of fused bicyclic heteroaromatics by organo-Mg reagents (RMgX)

In 2017, Provot and co-workers developed an efficient Kumada coupling reaction between chlorovinyl benzothiophene **160** and Grignard reagent **161** in the presence of Fe(acac)<sub>3</sub> (10 mol%) in THF at -30 °C leading to the highly substituted benzothiophene **162** in good yields (Scheme 49).<sup>149</sup>

Knochel and co-workers have shown that similar to Fe(III) catalysis, chemoselective cross-coupling reactions of the Kumada type can also be carried out using catalytic amounts of chromium(II) chloride (Scheme 50).<sup>150</sup> Thus, substrates considered challenging such as isoquinoline and quinoline derivatives **163** were successfully coupled with a wide range of functionalized aryl(heteroaryl)-Grignard reagents **164** in the presence of CrCl<sub>2</sub> (3 mol%). These reactions, which led exclusively to the formation of the  $\alpha$ -arylated heterocycles **165** without significant amounts of homocoupling products, proceed rapidly within minutes at room temperature in cyclopentyl methyl ether (CPME). Several functional groups, including esters and acetals, are tolerated by this method and the



Scheme 49 Fe-Catalyzed Kumada coupling for the synthesis of 2,3-disubstituted benzothiophene derivatives.

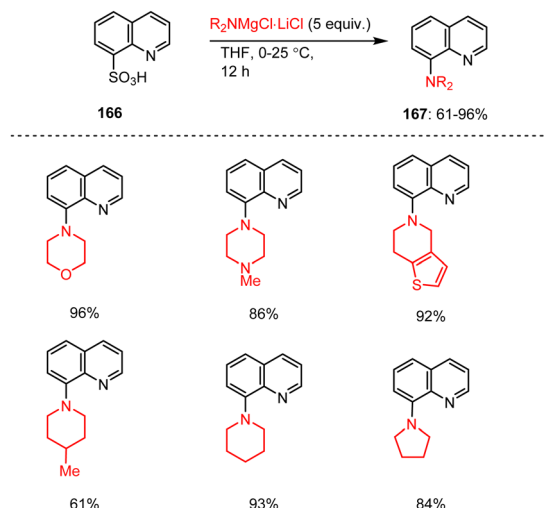


Scheme 50 CrCl<sub>2</sub>-Catalyzed cross-couplings of 2-quinolynyl halides with ArMgX.

required chromium salts can be successfully separated after the reaction using solid supports.

Later, the research group also developed a strategy for the transition metal-free amination of 8-quinoline sulfonic acids **166** using magnesium amides of the type R<sub>2</sub>NMgCl-LiCl. Thus, numerous cyclic secondary amines were first successfully converted by *i*-PrMgCl-LiCl into the corresponding magnesium amides, which in turn reacted readily with the quinoline sulfonic acids under mild conditions and provided the desired aminoquinolines **167** in excellent yields (Scheme 51).<sup>151</sup> Aminoquinoline scaffolds derived from heteroaryl sulfonic acids are of major interest in pharmaceutical chemistry and drug development.

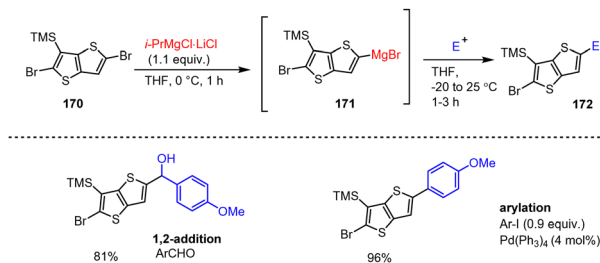
Steib *et al.* reported on a ligand-free Cr-catalyzed amination reaction of various N-heterocyclic quinoline and quinoxaline chlorides. The catalytic regioselective amination of 2-chloroquinolines, 1-chloroisoquinolines and 2,3-dichloroquinoxalines **168** with a



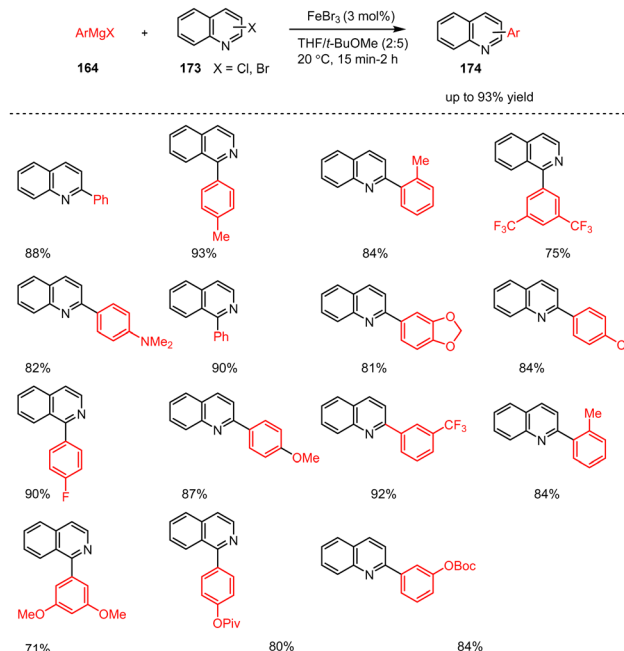
Scheme 51 Catalyst-free amination reaction of 8-quinoline sulfonic acid using magnesium amides.



A simple and practical method was developed by Kuzmina *et al.* using a non-toxic iron catalyst. This new approach for 2-substituted quinoline and isoquinoline scaffolds allowed smooth C(sp<sup>2</sup>)-C(sp<sup>2</sup>) cross-couplings of N-heterocyclic halides **173** with various electron-poor and electron-rich aryl



**Scheme 53** Preparation of functionalized thienothiophenes by reaction of heteroaryl magnesium reagents with electrophiles.



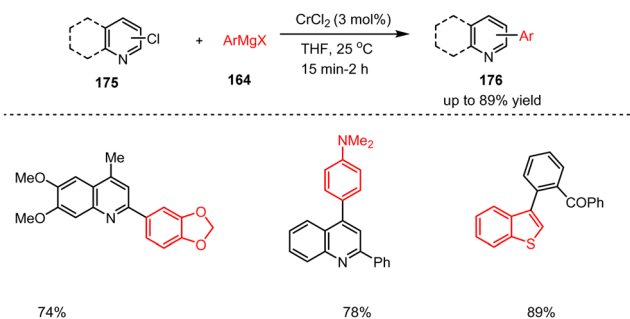
**Scheme 54** FeBr<sub>3</sub>-Catalyzed cross-coupling reactions of quinoline- and isoquinoline-based halides with functionalized organomagnesium reagents.

magnesium reagents (ArMgX, **164**) in the presence of FeBr<sub>3</sub> (3 mol%) (Scheme 54).<sup>154</sup> The inexpensive and efficient iron cross-coupling reaction was carried out in a mixture of THF and *t*BuOMe at 20 °C and turned out to be a key procedure for the preparation of highly functionalized N-heterocycles **174** in excellent yields with no formation of undesired homocoupling by-products. Thus, organomagnesium reagents with a variety of sensitive functional groups such as F, Cl, CF<sub>3</sub>, OPiv, OBoc, OMe, Me, and NMe<sub>2</sub> were successfully employed in this method. The resulting quinolines and heterocyclic derivatives thereof have shown major promise for the treatment of several diseases, including inflammation, cancer, diabetes, and malaria, as well as for various viral infections.

In 2013, Knochel and co-workers published a simple and efficient catalytic process for the preparation of 2- or 4-substituted heterocyclic quinoline motifs **176**. Using CrCl<sub>2</sub> (3 mol%) catalyst, N-heterocyclic chlorides **175** could be successfully used in a Kumada cross-coupling reaction with aryl(het)-magnesium reagents **164** under sustained conditions. When operated for 15 min up to 2 h in THF at 25 °C, this technique provided substituted quinolines **176** with good yields of up to 89% (Scheme 55).<sup>155</sup>

In addition, the same group reported the serendipitous discovery that the addition of quinoline or isoquinoline dramatically increased the rate and yield of Fe- and Co-catalyzed cross-coupling reactions. This ligand acceleration allowed the general scope of the described cross-coupling reactions to be extended to complex functional groups and the formation of heteroaryl-heteroaryl bonds, where the desired products were previously obtained at very low yields. For example, by using

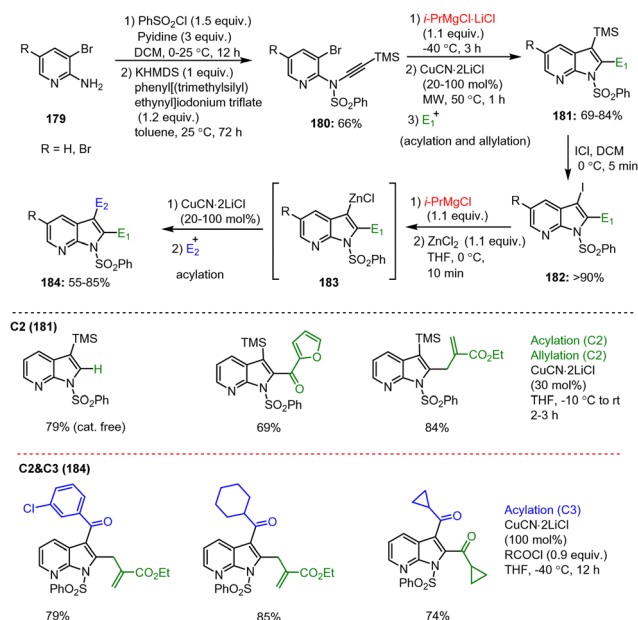




**Scheme 55** CrCl<sub>2</sub>-Catalyzed coupling reaction of quinoline-based chlorides with arylmagnesium reagents.

CoCl<sub>2</sub> (3 mol%) as a catalyst in the presence of isoquinoline (10 mol%), functionalized aryl and heteroaryl Grignard reagents **164** were successfully coupled with Br-, Cl-substituted quinolines **177** in reasonable yields (Scheme 56).<sup>156</sup>

Starting from easily accessible bromoaniline derivatives **179**, Frischmuth *et al.* investigated a mild and efficient intramolecular Cu-mediated carbomagnesiation method for the preparation of functionalized 4-azaindoles of type **181**. Subsequent further functionalization of these 4-azaindoles with various electrophiles thus provided access to highly functionalized N-heterocycles of type **184** in excellent yields of 74–85%. The preparation of key magnesium intermediates **180** for intramolecular cyclization was carried out by halogen-metal exchange reactions using *i*-PrMgCl-LiCl, tolerating a broad spectrum of functional groups in the substrate. Starting from TMS-containing heterocyclic precursor **181**, which is available in a few steps, the 3-iodoazaindole **182** was prepared by treatment with ICl, and then subjected to the halogen-metal exchange followed by an electrophilic scavenging reaction with acid chlorides. The corresponding, highly functionalized



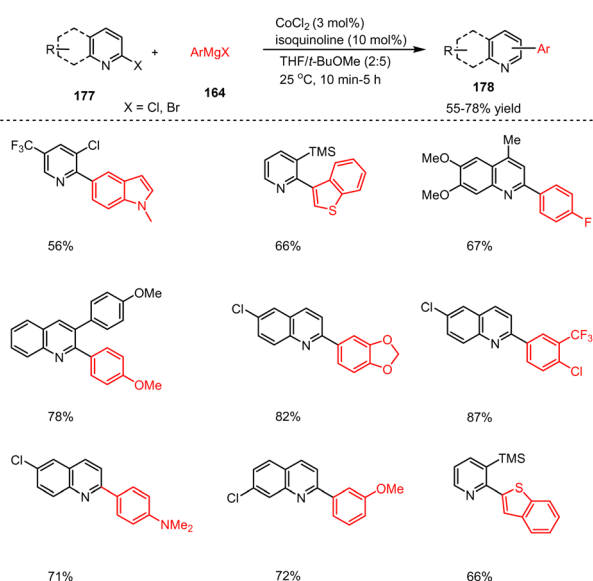
**Scheme 57** Synthesis of 2,3-disubstituted 7-azaindoles using *i*-PrMgCl.

4-azaindole ketones **184** were obtained in reasonable amounts (Scheme 57).<sup>157</sup>

Barl *et al.* reported the complete functionalization of the 7-azaindole scaffold **188** using the following reaction sequence: halogenation, cyclization, directed metalation, and halogen/Mg as well as sulfoxide/Mg exchange. By using this procedure, a complex and fully functionalized 7-azaindole **197** was obtained starting from the commercially available aniline derivative **185** *via* sequential transformation of the corresponding substituted key intermediate **188** (Scheme 58).<sup>158</sup> Using *n*-BuLi, TMPLi and *i*-PrMgCl as key metalating reagents, this multistep protocol afforded the desired key azaindole structure **197** with moderate yields and high tolerance of functional groups.

In 2013, Knochel and co-workers developed a formal regioselective C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling of substituted pyridines and quinoline derivatives **198** *via* mild BF<sub>3</sub>·OEt<sub>2</sub>-mediated nucleophilic addition reaction of Grignard or organozinc reagents, followed by chloranil-mediated oxidative aromatization. The high regioselectivity and broad tolerance towards functional groups make this method very valuable for the preparation of polyfunctional pyridines and quinolines **199** (Scheme 59).<sup>159</sup> Moreover, these reactions can be easily carried out on a larger scale with no reduction in yield.

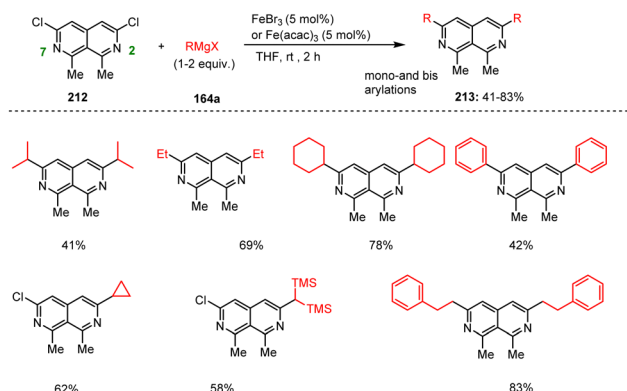
A general and mild intramolecular method for a copper-mediated carbomagnesiation reaction was presented by Nickel *et al.*, which can be used to synthesize functionalized N-heterocycles such as pyrrolo[2,3-*d*]pyrimidines **201** and azaindole derivatives **208**. In this work, pyrrolo[2,3-*d*]pyrimidines were prepared from metalated pyrrolo[2,3-*d*]pyrimidines, which in turn were accessible by treatment of *N*-alkynyl-5-iodo-6-sulfamido-pyrimidines with *i*-PrMgCl-LiCl, followed by transmetalation with CuCN·2LiCl and intramolecular carbocupration. Finally, the desired polyfunctional pyrrolo[2,3-*d*]pyrimidines **200** were obtained after an electrophilic quenching



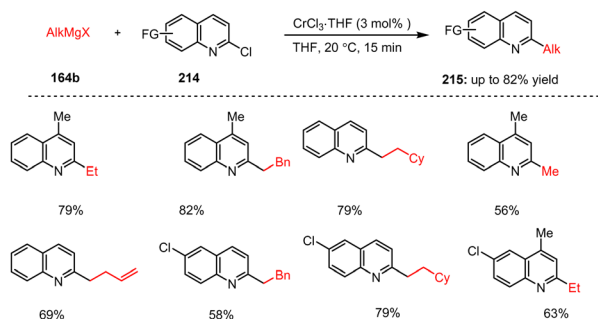
**Scheme 56** Co-Catalyzed Kumada coupling of 2-quinonyl halides.





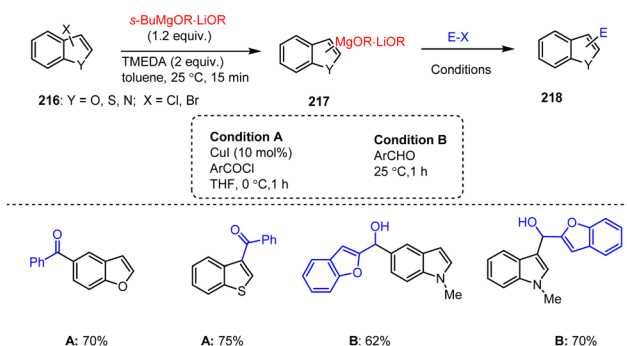


**Scheme 62** Fe-Catalyzed cross-couplings of the 1,8-dimethylnaphthyridine with alkyl Grignard reagents.



**Scheme 63** Cr(III)-Catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) Kumada coupling reactions of alkylmagnesium reagents with 2-chloroquinoline.

used exchange reagent  $s\text{Bu}_2\text{Mg} \cdot 2\text{LiCl}$ , but also about 110 times faster than those with Turbo-Grignard ( $i\text{-PrMgCl} \cdot \text{LiCl}$ ). In addition, the resulting Grignard reagents of the type  $\text{ArMgOR} \cdot \text{LiOR}$  or  $\text{HetArMgOR} \cdot \text{LiOR}$  can be easily added to ketones and acyl chlorides to form **218**-type reaction products under mild conditions (Scheme 64).<sup>164</sup> The synthesis of Grignard reagents in hydrocarbons or toluene is of great interest, as these weakly coordinated Grignard reagents can exhibit unusual reactivity and are also considered as industry-friendly reagents.

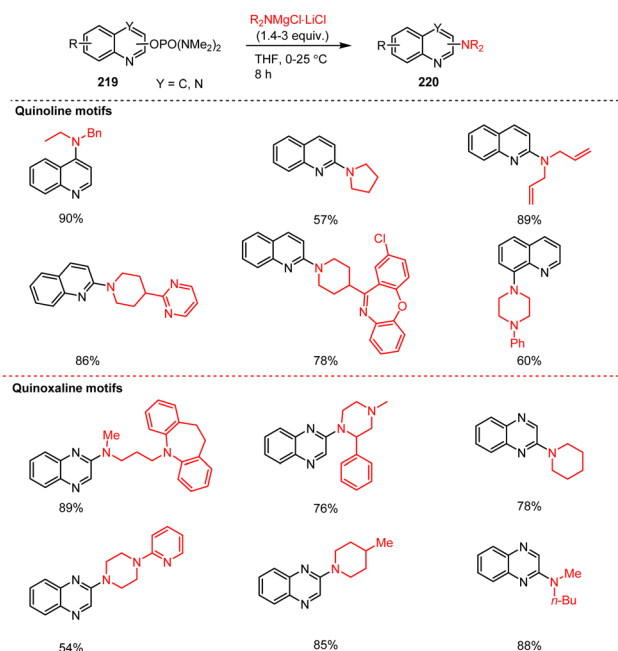


**Scheme 64** Functionalized fused heteroarenes via Br/Mg-exchange reaction and quenching with electrophiles.

Aminated N-heterocycles play an important role in modern pharmaceutical chemistry, which makes the development of synthetic protocols for their efficient preparation very attractive. In 2018, Knochel and colleagues presented the amination of phosphorodiamidate-substituted quinolines and quinoxalines with the magnesium amides  $\text{R}_2\text{NMgCl} \cdot \text{LiCl}$  under catalyst-free conditions. Here, 2-, 4- and 8-hydroxyquinoline and 2-hydroxyquinoxaline derivatives were converted to the corresponding phosphorodiamidates **219** and subjected to an amination reaction using various pharmaceutically active amines to give the fused N-heterocycles of type **220** (Scheme 65).<sup>165,166</sup>

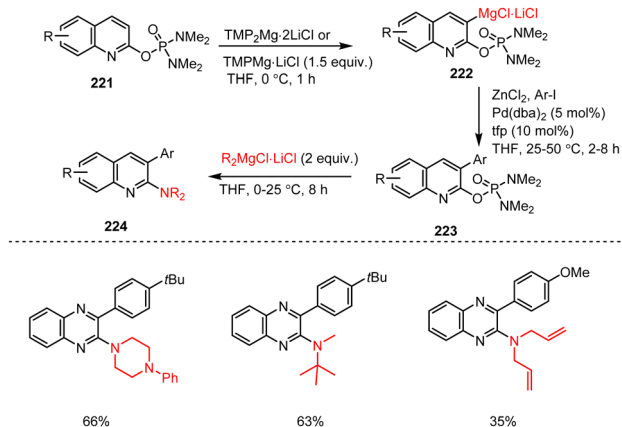
Since the phosphorodiamidate function is a strong direct metalating group (DMG), the amination can be combined with an *ortho*-functionalization step. Thus, several phosphorodiamidate-substituted N-heterocycles **221** were treated at 0 °C for 1 h with  $\text{TMPMgCl} \cdot \text{LiCl}$  or  $\text{TMP}_2\text{Mg} \cdot 2\text{LiCl}$  in THF. The type **222** Mg species formed were then either quenched with electrophiles such as  $\text{I}_2$  or  $(\text{BrCl}_2\text{C})_2$  or were successfully employed in Cu-catalyzed acylation reactions and Pd-catalyzed Negishi cross-couplings after Zn transmetalation steps. The resulting functionalized heterocycles **223** were finally subjected to the amination reaction that led to 2,3-difunctionalized quinoline derivatives **224** in 35–66% yields over two steps (Scheme 66).<sup>165</sup>

Sulfur-containing organic molecules are often useful building blocks in organic synthesis, which is why, transition metal-catalyzed desulfinative cross-coupling reactions are used to produce heterobiaryl products, for example. As these processes usually require high temperatures due to catalyst deactivation, milder and transition metal-free desulfination protocols are desirable. Along this line, Wei *et al.* presented a cross-coupling reaction of heteroaryl sulfinates with Grignard reagents for the



**Scheme 65** Synthesis of 2-amino quinoline and quinoxalines with  $\text{R}_2\text{NMgCl} \cdot \text{LiCl}$ .



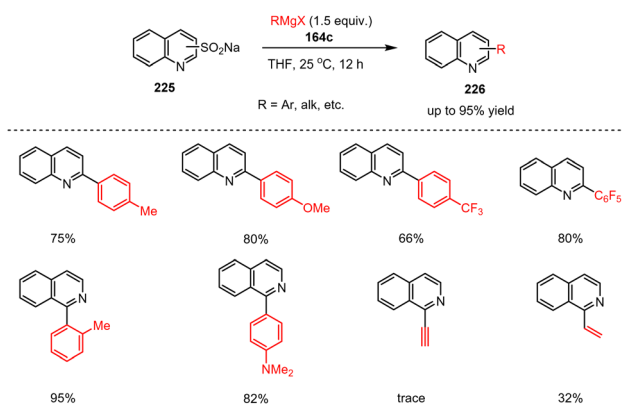


**Scheme 66** TMP-base mediated directed *ortho*-metalation and functionalization of various aryl phosphorodiamidates, followed by amination with  $R_2\text{NMgCl}\cdot\text{LiCl}$ .

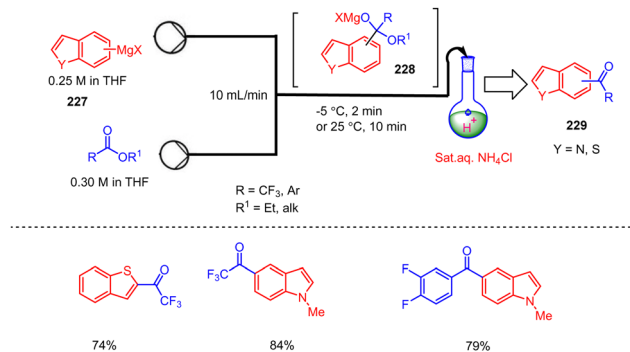
synthesis of heterobiaryls. Here, fused N-heteroaryl sulfonates **225** were reacted with functionalized aryl and alkyl Grignard reagents **164c** to produce quinoline-based biaryl heterocycles **226** under mild conditions (Scheme 67).<sup>167</sup> The transformation demonstrates great potential for the preparation of functionalized fused heteroaromatic compounds by utilizing quinoline and pyridine sulfonates as electrophilic starting materials for C–N cross-coupling reactions with no need for additional catalysts or bases.

A selective acylation protocol developed by the Knochel group for readily available heteroaryl magnesium reagents **227** and commercially available ester derivatives run at favourable temperatures (–5 to 25 °C) and short reaction times (2–10 min) under continuous flow conditions. The flow conditions prevent premature collapse of the hemiacetal intermediates despite non-cryogenic conditions, thereby providing satisfactory yields for heteroaryl ketones **229**. The coordination ability of the ester and aryl(het)magnesium reagents was decisive for the outcome of the acylation reaction (Scheme 68).<sup>168</sup>

Knochel, Bein and co-workers reported the selective functionalization of the 5-Br-substituted 1*H*-imidazo[1,2-*b*]pyrazole



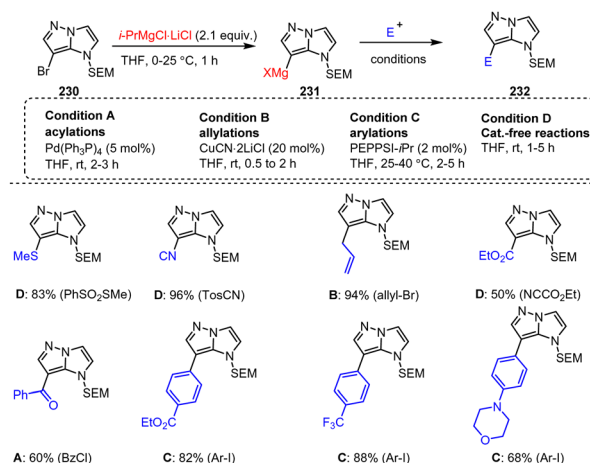
**Scheme 67** Transition-metal-free functionalization of heterocycles via desulfonative cross-coupling of quinolinyl sulfonates with aryl and alkyl Grignard reagents.



**Scheme 68** Synthesis of heteroaryl ketone using ester scaffolds and Grignard reagents.

scaffold **230** using a Br/Mg exchange reaction with *i*-PrMgCl in THF at r.t. The resulting reactive Mg intermediate **231** reacted with various commercially available electrophiles, such as by direct quenching with highly reactive electrophiles or by Pd-catalyzed cross-coupling as well as Cu-mediated acylation or allylation reactions. Overall, these sequences led to the formation of functionalized condensed N-heterocycles **232** in good to excellent yields (Scheme 69).<sup>137,169</sup>

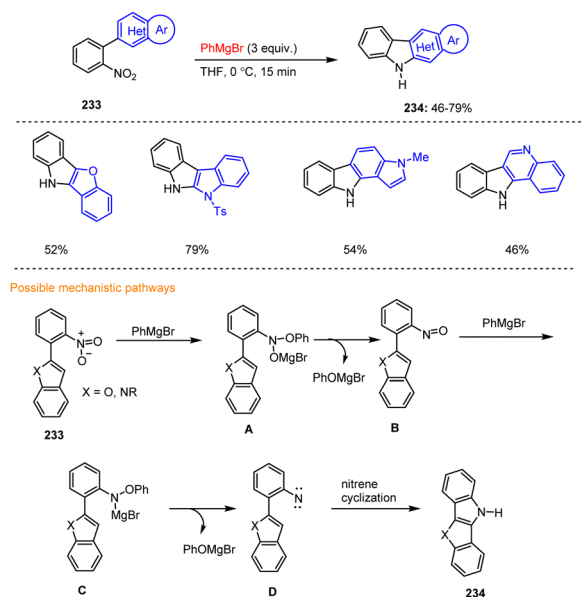
Kürti, Ess and co-workers have described an intramolecular amination of arene  $\text{C}(\text{sp}^2)\text{--H}$  bonds at low temperature, without the use of transition metals and with high regioselectivity. The reaction is operationally simple and scalable (1–10 mmol) and allows the formation of fused N-heterocycles **234** under mild conditions, using readily available 2-nitrobiaryls **233** and PhMgBr (Scheme 70).<sup>170</sup> Initially, the Grignard reagent attacks the nitro group of **233**, whereby a reactive aryl nitroso intermediate **B** is formed after elimination of magnesium phenolate. This species then reacts with a second equivalent of PhMgBr to form an aryl nitrene intermediate **D**, which cyclizes intramolecularly to the desired carbazole derivative **234**. This method also allowed the synthesis of the two bioactive carbazole alkaloids Clausin V and Glycoborin.



**Scheme 69** Selective functionalization of the brominated fused aromatic 1*H*-imidazo[1,2-*b*]pyrazole via Br/Mg exchange reaction with *i*-PrMgCl.



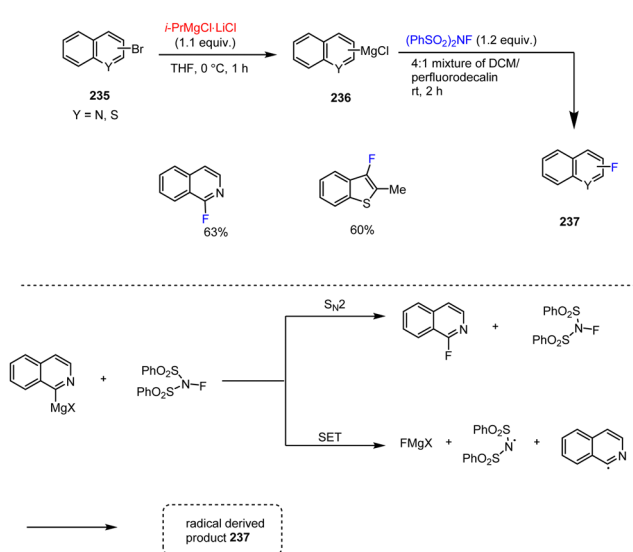




**Scheme 70** Highly regioselective synthesis of fused carbazoles using Grignard reagents.

In 2010, the group of Knochel and co-workers developed a simple and extremely versatile one-pot strategy for the preparation of organo-fluorine compounds by converting functionalized aryl halides **235** into aryl and heteroaryl fluorides **237**. This method enables efficient and direct, metal-free syntheses of fluorinated isoquinoline and benzothiophene derivatives as well as arylated fluorine compounds, which are otherwise difficult to prepare by the conventional catalytic methods (Scheme 71).<sup>171</sup>

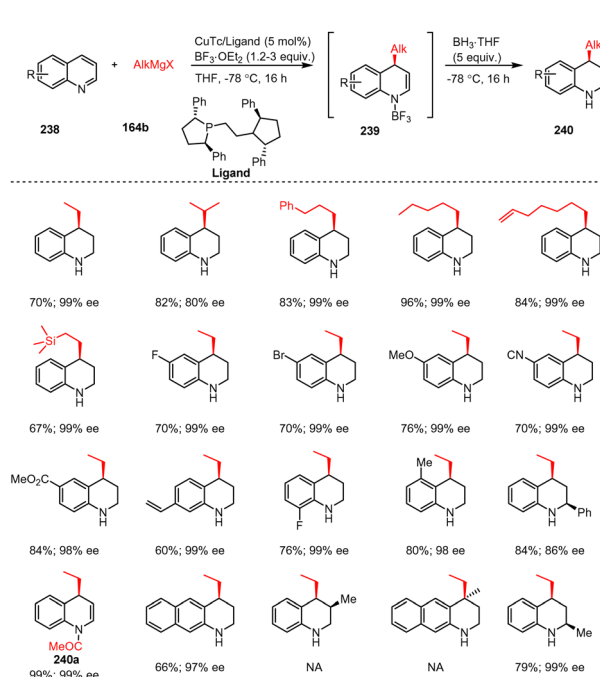
The dearomative functionalization of heteroaromatics is one of the most straightforward approaches for the synthesis of chiral heterocyclic systems, key building blocks for both



**Scheme 71** Electrophilic fluorination of heteroaryl magnesium reagents using NFSI.

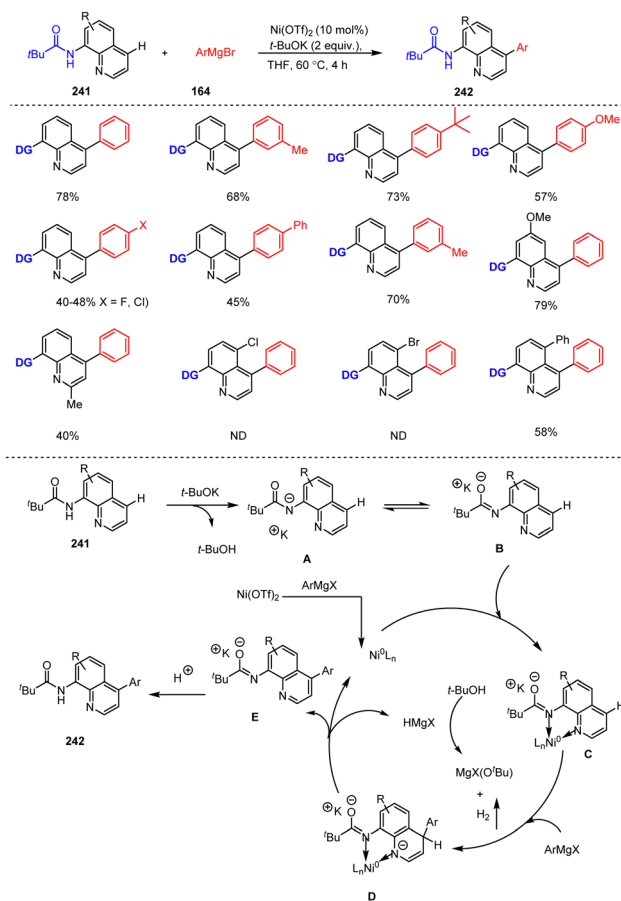
synthetic chemistry and drug discovery. Yan *et al.* have recently presented a catalytic system that enables the nucleophilic dearomatization of quinolines **238** in combination with organometallic compounds very efficiently. A synergistic combination of Lewis acid, chiral copper(I) catalyst, and Grignard reagent allows to overcome the energy barrier of dearomatization and to obtain chiral C-4 addition products **240** with almost absolute regio- and stereo-control. Remarkably, in a preparative reaction, the amount of chiral copper catalyst can be reduced to 0.1 mol%, leading to the highest turnover number (TON) reported so far in any enantioselective reaction with Grignard reagents. Molecular modelling suggests that the role of the Lewis acid is not only to activate the substrate towards potential nucleophilic addition, but also to subtly direct the regiochemistry, by preventing C-2 addition (Scheme 72).<sup>172</sup>

A convenient method for the synthesis of functionalized quinolines is based on site-selective modification by C–H functionalization of easily accessible quinoline scaffolds. An illustrative example of such an approach involving Ni-catalyzed C–H bond arylation of 8-aminoquinoline motifs at the distant C-4 position was presented by Qiu, Kambe and co-workers. The authors proposed the following reaction mechanism for this catalytic direct C–H arylation at C-4 of 8-aminoquinoline scaffolds: first, deprotonation of the quinolinylamide **241** with *t*-BuOK takes place, resulting after isomerization, in the formation of intermediate **B**. Its coordination to an *in situ* generated Ni(0) species leads to the key intermediate **C**, which then undergoes a nucleophilic addition of ArMgX to afford intermediate **D**. After HMgX elimination and subsequent protonation, the desired functionalized quinolines **242** are formed. The protocol shows a broad range of functional group tolerance to



**Scheme 72** Dearomative functionalization of quinoline position C-4 to access tetrahydroquinolines.



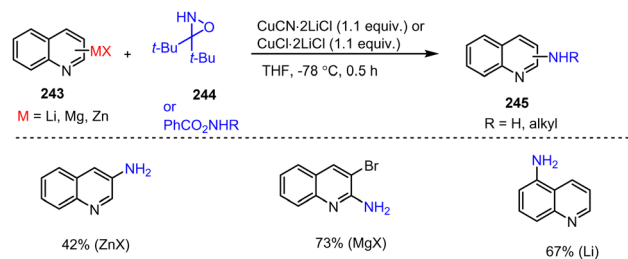


**Scheme 73** Ni-Catalyzed remote C(sp<sup>2</sup>)-H bond arylation of 8-amino protected quinolines.

various functionalized aryl Grignard reagents **164** and aminoquinoline motifs **241** providing the desired arylated products **242** in good to excellent yields (Scheme 73).<sup>173</sup> As a result, rapid access to bioactive and multi-substituted aminoquinolines is made possible.

A practical and efficient solution for the direct amination of heteroaryl Li, Mg and Zn reagents, which has long been considered difficult, was developed in Kürti's group. Heteroaryl organometallics such as quinoline derivatives **243** could be converted to the desired amination products in the absence of directing groups by using an oxaziridine or hydroxylamine reagent **244** in the presence of Cu(I) salts. This new approach for direct electrophilic amination thus seems to represent a general yet simple method that could be used for the efficient production of many structurally complex active pharmaceutical compounds and natural products (Scheme 74).<sup>174</sup>

Recently, Harutyunyan's group developed a simple and chemoselective asymmetric addition protocol for the efficient construction of chiral heterocyclic molecules of type **247**. Using readily available Grignard reagents **164b** and an activating Lewis acid (BF<sub>3</sub>·OEt<sub>2</sub>), a wide range of β-substituted conjugated alkenyl-N-heteroaromatics **246** could be chemo- and enantioselectively alkylated by copper-catalyzed conjugate addition. This synthetic protocol is of particular interest for applications in medicinal chemistry as it allows the introduction of linear,

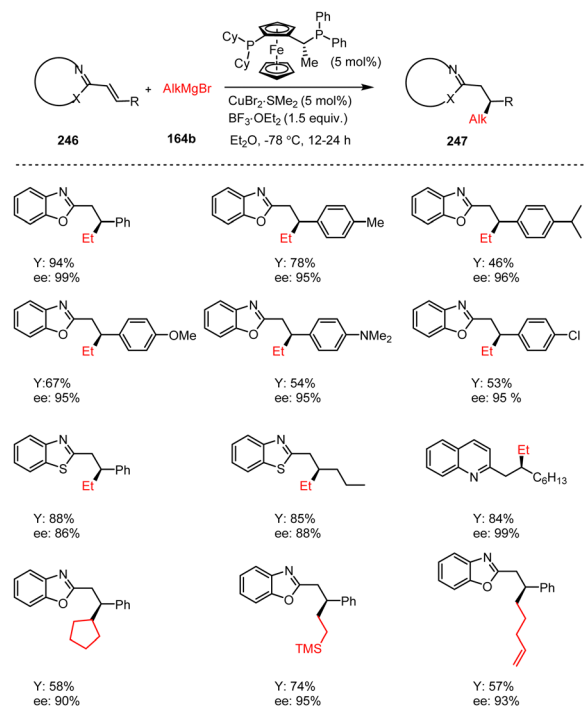


**Scheme 74** Amination of structurally diverse heteroaryl-based organo-metallic reagents.

branched, and cyclic alkyl chains as well as a phenyl group at the β-carbon position of the alkenyl N-heteroaromatic compounds. The overall synthetic success depends largely on the interplay of the substrate-activating Lewis acid and the use of highly reactive Grignard reagents in the presence of a diphosphine-stabilized copper catalyst (Scheme 75).<sup>175</sup>

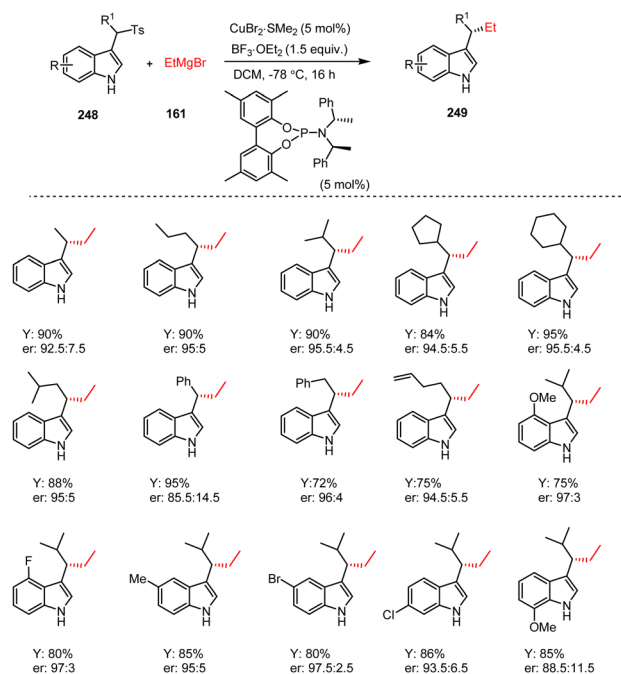
The same group subsequently reported a related reaction in which alkyl Grignard reagents **161** are added enantioselectively under mild conditions to vinylogous imines synthesized *in situ* from sulfonylindoles **248**. In the presence of a copper(I) salt and a chiral phosphoramidite ligand, high yields, and enantiomeric ratios of chiral 3-sec-alkyl-substituted indoles **249**, which are important structural elements of several drugs and alkaloids, can be obtained (Scheme 76).<sup>176</sup> In addition, the reaction can also be conducted on a larger scale with only 1 mol% of the catalyst and with no loss of yield or enantiomeric purity of the product.

In addition to indole motifs, substituted benzofuran scaffolds, *e.g.* **251**, are also important structural elements in

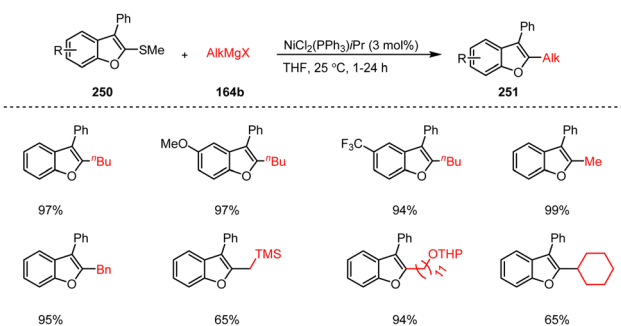


**Scheme 75** Catalytic asymmetric conjugate addition of alkyl Grignard reagents to alkenyl-substituted benzothiazole and benzoxazole.





**Scheme 76** Cu-Catalyzed enantioselective addition of ethyl Grignard reagents to indole-derived vinylogous imines.

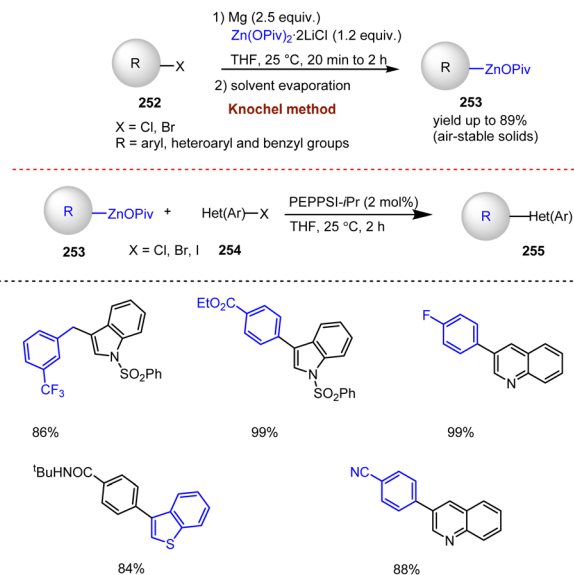


**Scheme 77** Ni-Catalyzed Kumada cross-coupling of 2-thiomethyl benzofurans with alkyl Grignard reagents.

pharmacologically active compounds, for instance in protein tyrosine phosphatase inhibitors. Thus, Baralle *et al.* successfully demonstrated an efficient cross-coupling reaction between branched alkyl Grignard reagents **164b** and 2-thiomethylbenzofurans **250** employing a Ni-NHC (Ni-N-heterocyclic carbene) complex as the catalyst. Even 3-(4-biphenyl)-2-alkylbenzofurans can be assembled in one step employing reaction, rendering such compounds accessible in a diversity-oriented manner to be used as intermediates for the preparation of PTP 1B inhibitors (Scheme 77).<sup>177</sup>

## 5 Organozinc-mediated functionalization of fused bicyclic heteroaromatics and their scaffolds

Organozinc reagents are well known for their transmetalation abilities and excellent tolerance towards functional groups.



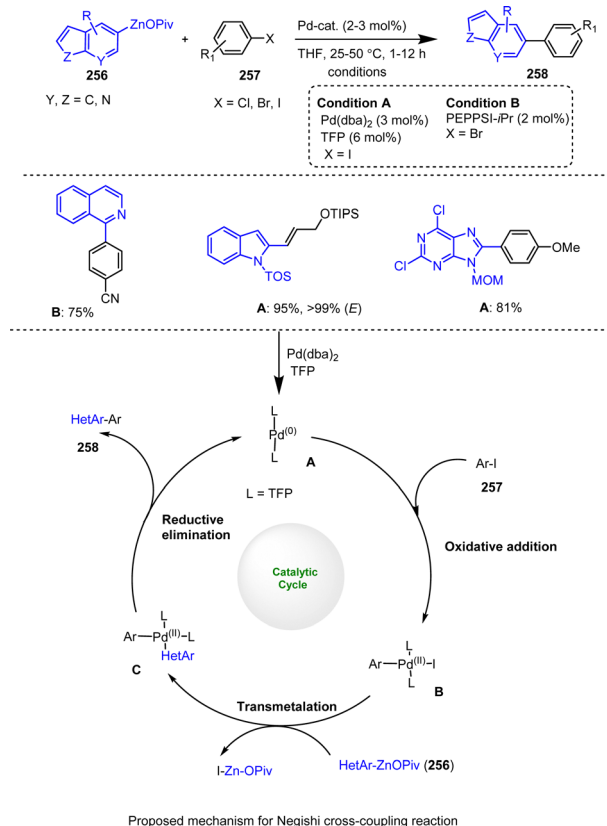
**Scheme 78** Pd-catalyzed C(sp<sup>2</sup>)-C(sp<sup>2</sup>)-cross-coupling of solid aryl, heteroaryl and benzylic organozinc pivalates with aryl electrophiles.

Organozinc pivalates (RZnOPiv) have been reported as salt-stabilized solid aryl, heteroaryl and benzylic organozinc compounds, which not only exhibit improved resistance to air and moisture, but also show excellent reactivity in Negishi cross-coupling and carbonyl addition reactions. These organozinc compounds are prepared in a one-pot process under mild conditions from aryl and heteroaryl halides (Br, Cl) as well as benzyl chlorides **252** using Mg and Zn(OPiv)<sub>2</sub>·2LiCl (Scheme 78).<sup>178</sup> The solid materials **253** obtained after evaporation of the solvent can be stored at room temperature under argon for months and may even be exposed to air for short periods.

In a subsequent study, the pool of solid organozinc pivalates was further expanded and their stability in air was improved while their reactivity in Negishi cross-coupling reactions was maintained. The decisive factor here was the use of a directed metalation procedure of arenes and heteroarenes with TMPMgCl·LiCl followed by transmetalation with Zn(OPiv)<sub>2</sub> (Scheme 79).<sup>179</sup> The Pd-catalyzed Negishi cross-coupling reaction of aryl halides **257** with heteroaryl-zinc reagents generates the depicted intermediates **A-C** by means of the well-known reaction sequence of initial oxidative addition to **B**, subsequent transmetalation with HetAryl-ZnOPiv **256** to form the key intermediate **C** and final reductive elimination to the desired cross-coupling product **258**. This protocol also yielded fine powdered organozinc pivalates **256** that were easy to handle after evaporation of the solvent and that retained most of their activity (> 85%), even when exposed to air for 4 h. Moreover, they could be readily used in Negishi cross-coupling reactions with a wide range of electrophiles **257** employing technical grade solvents, which is particularly important for industrial applications.

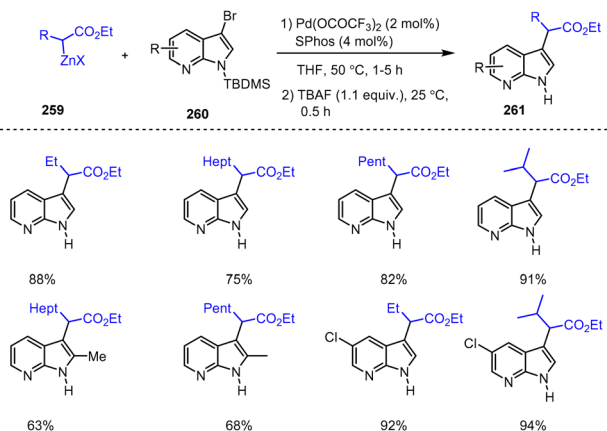
Barl *et al.* introduced a method for the functionalization of 7-azaindole *via* a cross-coupling reaction with alkylzinc



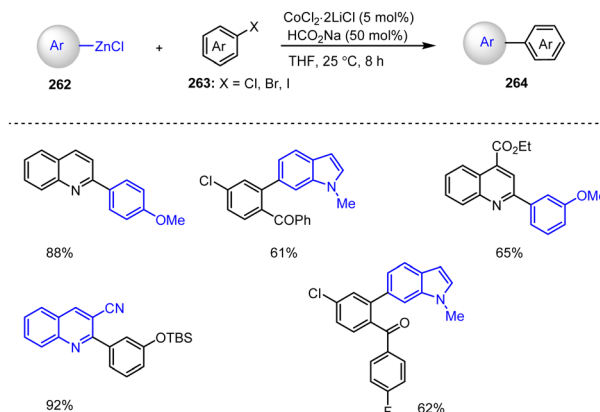


**Scheme 79** C(sp<sup>2</sup>)-C(sp<sup>2</sup>) cross-coupling reaction of solid and air-stable organozinc reagents and addition of electrophiles enabled by palladium catalysts.

reagents. Thus, by using a Pd-catalyzed Negishi reaction between the Reformatsky-type reagents **259** and silyl protected 3-bromo-7-azaindoles **260**, targeted 7-azaindole carboxylic acid ester derivatives **261** were formed. Final TBAF-mediated removal of the TBDMS protecting group in THF at 0 °C afforded 2-(7-azaindolyl) carboxylic acid esters **261** in high yields of up to 94% (Scheme 80).<sup>180</sup>



**Scheme 80** Pd-Catalyzed C(sp<sup>2</sup>)-C(sp<sup>3</sup>)-cross-coupling of 7-azaindoles and Reformatsky-type reagents.

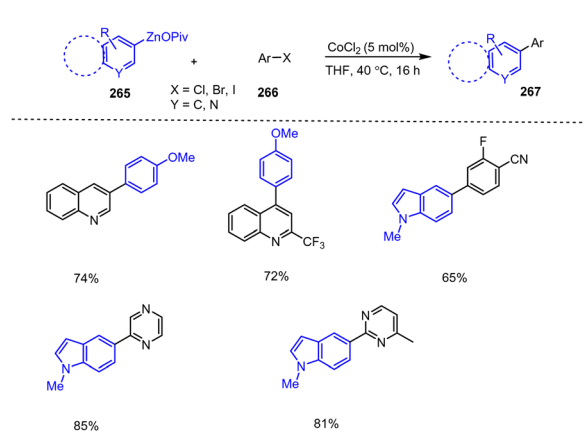


**Scheme 81** Co-Catalyzed cross-coupling reaction of aryl halides and organozinc reagents.

A simple, cobalt-catalyzed procedure for the carbon-carbon coupling of halogenated ketones and N-heterocyclic chlorides/bromides **262** with various (hetero)aryl zinc reagents **263** was developed by Haas *et al.* (Scheme 81).<sup>181</sup> Different electron-poor and electron-rich functionalized aryl zinc reagents were successfully coupled within a few hours at room temperature under the reported conditions. Moreover, the use of sodium formate HCO<sub>2</sub>Na (50 mol%) proved to be decisive for the success of these cross-coupling reactions.

According to Hammann *et al.*, the previously described air- and moisture-stable aryl and heteroaryl zinc pivalates **265** can also be successfully subjected to Co-catalyzed cross-coupling reactions with various aryl and heteroaryl halides **266**. The proposed method is again characterized by its broad applicability, as both electron-rich and electron-poor electrophiles are tolerated in the presence of CoCl<sub>2</sub>. Thus, the corresponding reactions of 5-indolylzinc pivalate with 2-bromopyrimidine or 2-chloropyrazine, for example, proceeded in good yields (Scheme 82).<sup>182</sup>

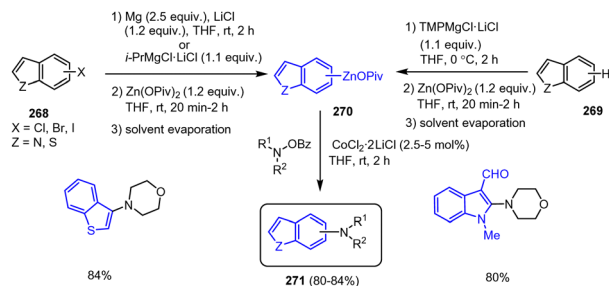
Cobalt-catalyzed electrophilic amination reactions of organozinc pivalates with *O*-benzoylhydroxylamines under mild and sustained reaction conditions were first published by Chen



**Scheme 82** Broadly applicable and robust Co-catalyzed cross-coupling reaction of functionalized organozinc pivalates with aryl halides.







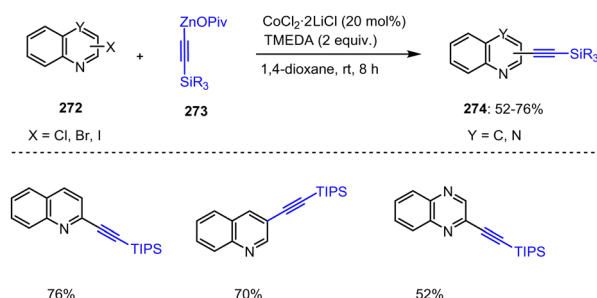
**Scheme 83** Co catalyzed amination of heteroaryl zinc pivalates with various *O*-benzoyl-hydroxylamines and anilines.

*et al.* Under the described reaction conditions, C–N cross-couplings between *N*-hydroxylamine benzoates and heteroaryl zinc pivalates **270** could be carried out at 25 °C within 2–4 h in the presence of  $\text{CoCl}_2 \cdot 2\text{LiCl}$  (2.5–5.0 mol%), yielding the corresponding tertiary (hetero-) arylated amines in good amounts (Scheme 83).<sup>183</sup> In addition, this method provides access to pharmacologically relevant diarylamine and aryl(heteroaryl)amine units. For example, a clinical candidate for the treatment of tuberculosis was synthesized using this Co-catalyzed amination protocol as the key step.

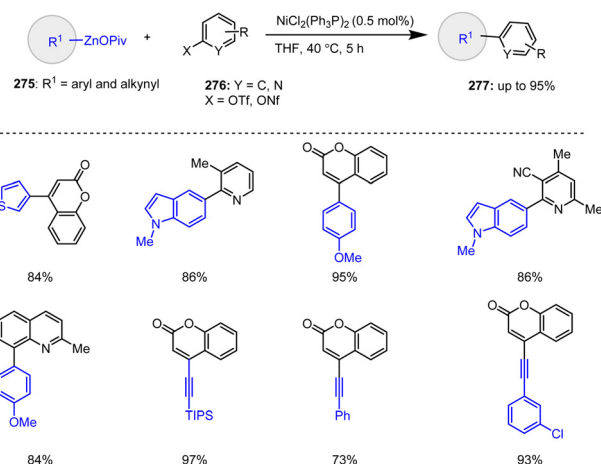
In 2017, Hammann *et al.* delineated an improved method for the preparation of air-stable silyl group-protected alkynyl zinc reagents **273** that can be successfully employed in  $\text{CoCl}_2$ -catalyzed  $\text{C}(\text{sp}^2)\text{--C}(\text{sp})$  coupling reactions with various heteroaryl halides **272**. The described process can be used to functionalize various biologically important heterocyclic scaffolds, such as quinoxalines and quinoline analogs **274** under sustainable conditions with acceptable yields, while incorporating synthetically beneficial alkyne residues (Scheme 84).<sup>184</sup>

In 2019, Ni-catalyzed  $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^2)$  and  $\text{C}(\text{sp}^2)\text{--C}(\text{sp})$  cross-coupling reactions between functionalized heteroaryl zinc pivalates **275** and various heteroaryl triflates as well as nonaflates **276** were reported with good to excellent yields. It is noteworthy that only 0.5 mol% of the Ni catalyst was required for these Negishi cross-couplings in THF at 40 °C (Scheme 85).<sup>185</sup>

Organozinc pivalates are also useful reagents for the late-stage functionalization of small peptides and cyclopeptides by means of Negishi cross-coupling reactions. For example, Leroux *et al.* were able to successfully couple peptides **278** containing tyrosine or phenylalanine scaffolds with highly functionalized



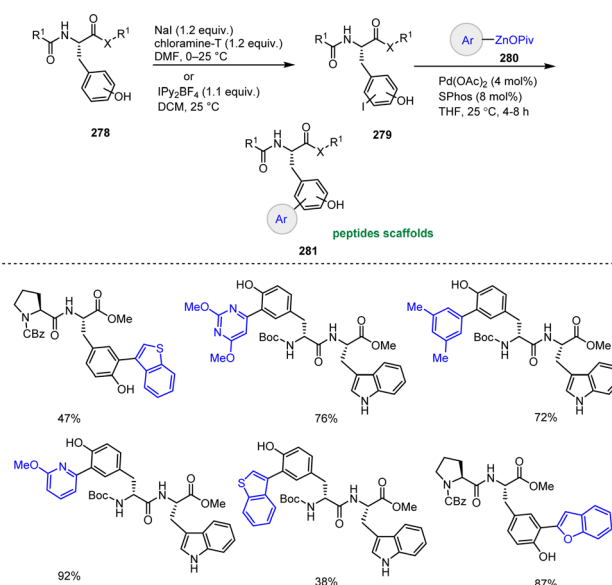
**Scheme 84**  $\text{CoCl}_2$ -catalyzed  $\text{C}(\text{sp}^2)\text{--C}(\text{sp})$ -cross-coupling reaction of silyl-protected alkynylzinc pivalates with heteroaryl halides.



**Scheme 85** Ni-Catalyzed Negishi cross-coupling of aryl and heteroaryl zinc pivalates with heteroaryl triflates.

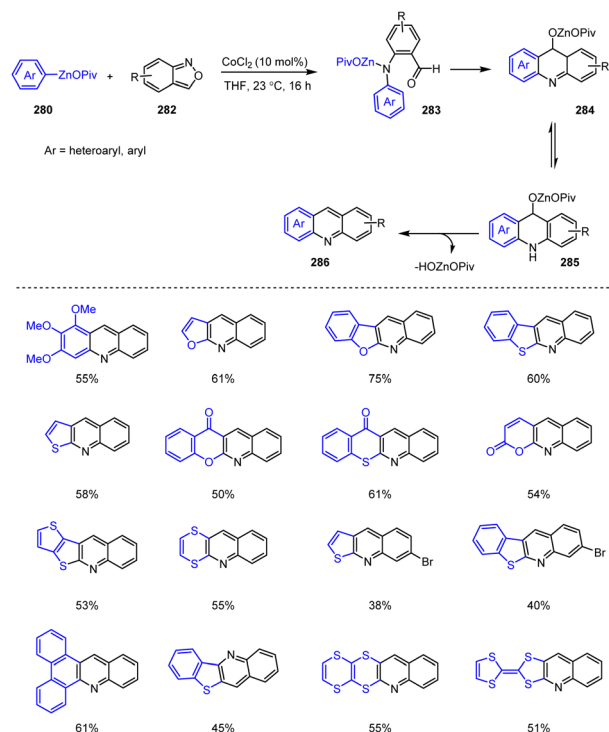
aryl and heteroaryl organozinc reagents under Pd catalysis. For this purpose, the corresponding readily available iodotyrosine- or iodophenylalanine-containing peptides **279** were site-specifically reacted with the respective organozinc pivalates **280** in the presence of the Pd catalyst in THF at 25 °C for 4–8 h to provide the modified target peptides **281** (Scheme 86).<sup>186</sup>

Cobalt-catalyzed electrophilic amination reactions of anthranilic derivatives **282** with functionalized aryl, heteroaryl, alkenyl and alkyl zinc pivalates **280** can be used to produce complex, condensed N-heterocyclic scaffolds **286** under mild conditions. Li *et al.* were able to show that the aniline derivatives **283** initially resulting from Co-catalyzed amination reactions can be cyclized under acidic conditions within a cascade reaction to form new complex, condensed quinolines (Scheme 87),<sup>187</sup> some of which are of interest for materials



**Scheme 86** Pd-Catalyzed late-stage functionalization of cyclopeptides and peptides with (hetero)aryl zinc reagents.



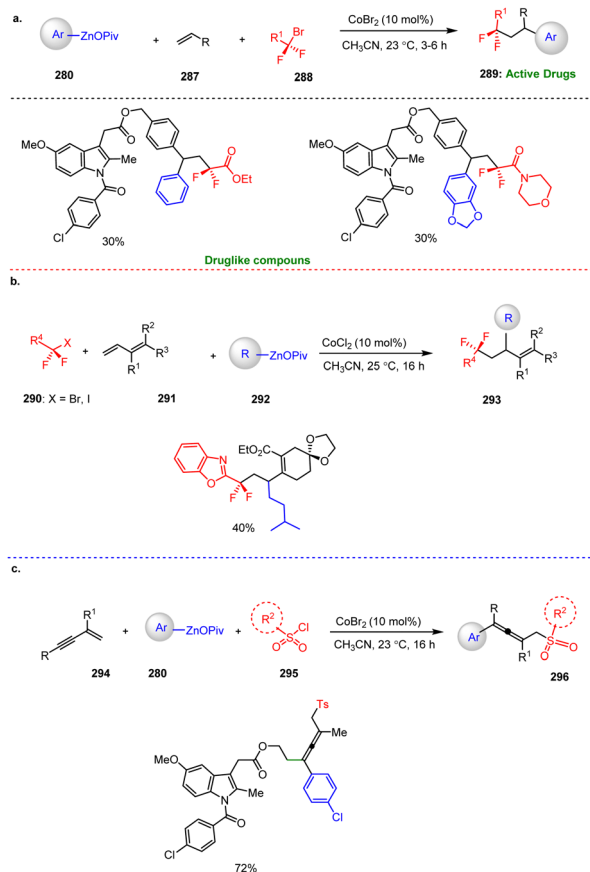


**Scheme 87** Co-catalyzed domino cascade amination reactions of aryl-zinc reagents with anthranil derivatives.

science applications such as organic light-emitting diodes or semiconductors in perovskite solar cells due to their promising properties.

Recently, Lei, Li and co-workers presented a method for the regioselective difluoroalkylarylation of alkenes and 1,3-dienes using functionalized aryl zinc pivalates **280** and difluoroalkyl bromides **288** in the presence of a cobalt catalyst. This one-pot three-component cross-coupling reaction can be used to form difluoroalkylarylated products with predictable regioselectivity and high diastereoselectivity by cascade-like C(sp<sup>3</sup>)-C(sp<sup>3</sup>) and C(sp<sup>3</sup>)-C(sp<sup>2</sup>) bond formations. With activated and non-activated alkenes **287**, the reaction proceeds under remarkably mild conditions with a broad range of substrates using user-friendly solid zinc reagents of excellent functional group tolerance. The process is therefore of particular interest for pharmaceutical applications and late-stage functionalization of drug candidates, as it is easily scalable and allows access to *e.g.*, difluorinated indole scaffolds **289** (Scheme 88a).<sup>188a</sup>

In addition, the preparation of solid, salt-stabilized branched alkyl-zinc reagents of the alkyl-ZnOPiv and R<sub>3</sub>Si-ZnOPiv type was reported. Due to OPiv coordination, these reagents exhibited not only enhanced stability but also increased reactivity in Co-catalyzed difluoroalkylation reactions of dienates, allowing modular, site-selective installation of CF<sub>2</sub> and C(sp<sup>3</sup>) groups to the double bonds. The twofold C(sp<sup>3</sup>)-C(sp<sup>3</sup>) cross-couplings of **291** proceeded under mild conditions and were characterized by a broad substrate spectrum and high compatibility with functional groups, thereby enabling an



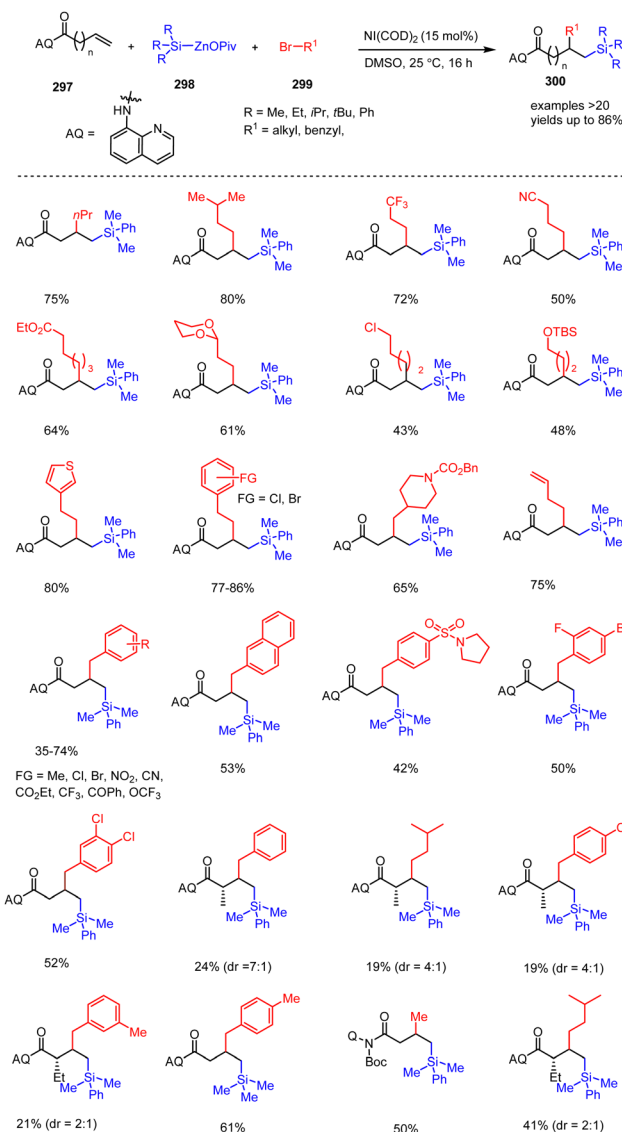
**Scheme 88** Fluoroalkylarylation of drugs scaffolds by cobalt catalysis and organozinc pivalates.

efficient late-stage functionalization of bioactive molecules and fluorinated products **293** (Scheme 88b).<sup>188b</sup>

Furthermore, both salt-stabilized aryl and alkyl zinc pivalates **280** show superior reactivity for the cobalt-catalyzed 1,4-carbosulfonylation of 1,3-enynes **294** with sulfonyl chlorides **295** compared to conventional halide-supported organozinc reagents. In this way, highly functionalized  $\alpha$ -allene sulfones **296** can be easily and selectively produced *via* the cascade formation of C-C/C-S bonds leading *inter alia* to functionalized bioactive indole scaffolds (Scheme 88c).<sup>188c</sup>

A new method for the preparation of solid, air-stable silyl zinc pivalates from the corresponding silyl lithium reagents by transmetalation with Zn(OPiv)<sub>2</sub> was recently presented by Li and co-workers. The resulting organosilyl zinc pivalates **298** could be successfully used for the silylative difunctionalization of alkenes. Using a convenient chelate-assisted Ni-catalyzed regioselective alkyl- and benzyl-silylation of 8-aminoquinoline-functionalized alkenes **297**, the corresponding highly functionalized alkyl silanes **300** could be generated in very good yields. As before, OPiv coordination proved to be crucial for improving the reactivity of the silyl zinc pivalates and provided access to alkyl silanes with a broad substrate spectrum and a high tolerance towards functional groups. The synthetic utility of this alkene carbosilylation sequence was again demonstrated



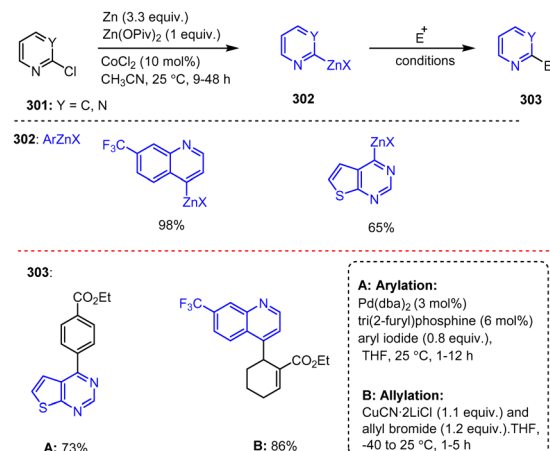


**Scheme 89** Catalytic applications of air-stable silylated zinc pivalates in nickel-catalyzed carbosilylation reactions of various olefins and alkyl halides.

by late-stage functionalizations of natural products and drug-like molecules as well as by simple, subsequent transformations of the resulting alkyl silanes (Scheme 89).<sup>189</sup>

A protocol for converting various readily available N-heteroaryl chlorides **301** into the corresponding organozinc reagents by Co-catalyzed zinc dust insertion in the presence of zinc pivalates in benzonitrile was reported by Kremsmaier *et al.* The resulting organozinc pivalates **302** were successfully reacted with a wide range of electrophiles, such as commercially available aryl halides or acid chlorides, employing Pd or Cu catalysts to give the targeted functionalized heteroarenes **303**, as presented in Scheme 90.<sup>190</sup>

Recently, Šebesta and co-workers presented a mechanochemical Negishi C(sp<sup>2</sup>)-C(sp<sup>2</sup>) cross-coupling reaction of aryl zinc pivalates **304** with aryl(heteroaryl) bromides **305** at room temperature under air. Using this simple Pd-catalyzed process,



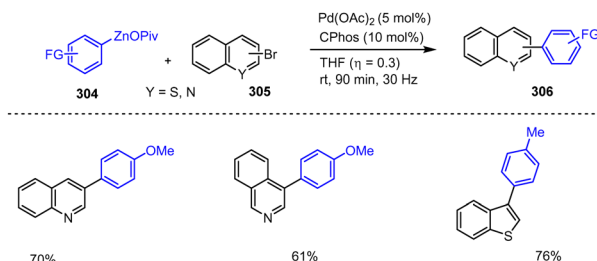
**Scheme 90** Synthesis of heteroaryl organozinc reagents enabled by cobalt catalysis for cross-coupling reactions.

quinoline and benzothienopyridine derivatives **306** were prepared in good yields and within a short time by ball milling. The reaction tolerates various functional groups and can be carried out on a useful preparative scale (Scheme 91).<sup>191</sup>

Melzig *et al.* reported the functionalization of various thiomethyl-substituted fused N-heterobicycles **307** (e.g., based on isoquinolines, quinazolines, benzothiazoles, or benzoxazole scaffolds) by nickel-catalyzed cross-coupling reactions with functionalized alkyl, aryl, heteroaryl, and benzylic zinc reagents **308**. These reactions can be carried out using an inexpensive catalytic system of Ni(acac)<sub>2</sub> and the DPE-Phos ligand at 25 °C, as shown in Scheme 92.<sup>192</sup>

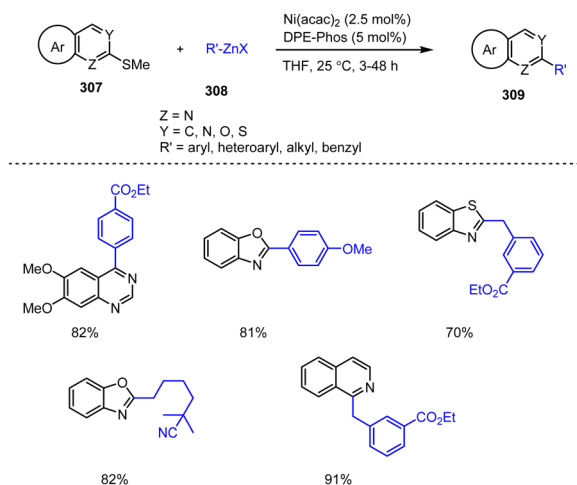
A mild Negishi cross-coupling of 2-pyridylorganozinc reagents **311** and heteroaryl chlorides **312** was described by Luzung, Patel, and Yin. Using catalytic amounts of Pd<sub>2</sub>(dba)<sub>3</sub> (2 mol%) and XPhos as the ligand, many examples of the desired heterocycles **313** were accessible in high yields, complementing the existing coupling reactions for 2-heterocyclic organometallic reagents. The organozinc reagents **311** required for this purpose can be generated *in situ* under Knochel conditions from 2-pyridyl bromides **310** and *i*-PrMgCl at room temperature (Scheme 93).<sup>193</sup>

Knochel's group has also developed a Ni-catalyzed cross-coupling of heteroaryl halides, including indole, quinoline and quinoxaline derivatives, with aminoalkyl zinc reagents **314** at room temperature. This method allows a convenient one-step

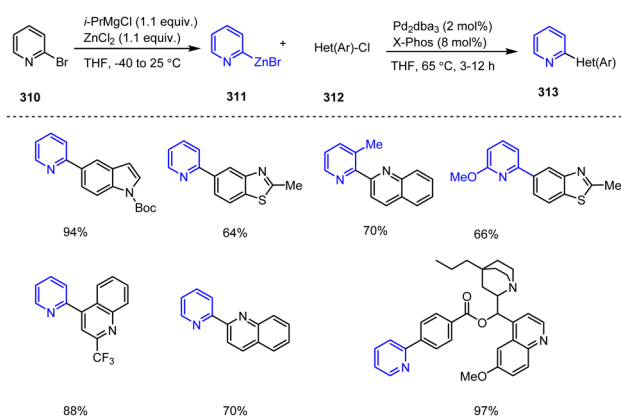


**Scheme 91** Mechanochemical Pd-catalyzed Negishi coupling reaction of aryl halides and organozinc pivalates.





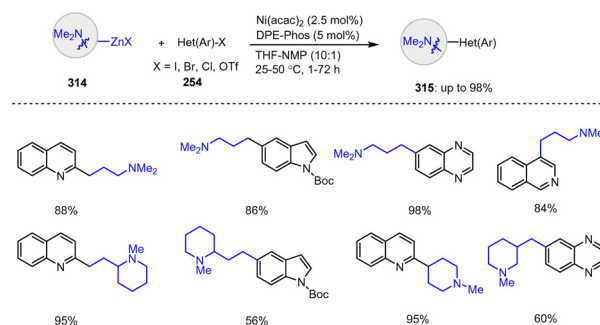
**Scheme 92** Ni-Catalyzed C(sp<sup>2</sup>)-C(sp<sup>2</sup>) and C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling reactions of thiomethyl-substituted bicyclic heterocycles with organozinc reagents.



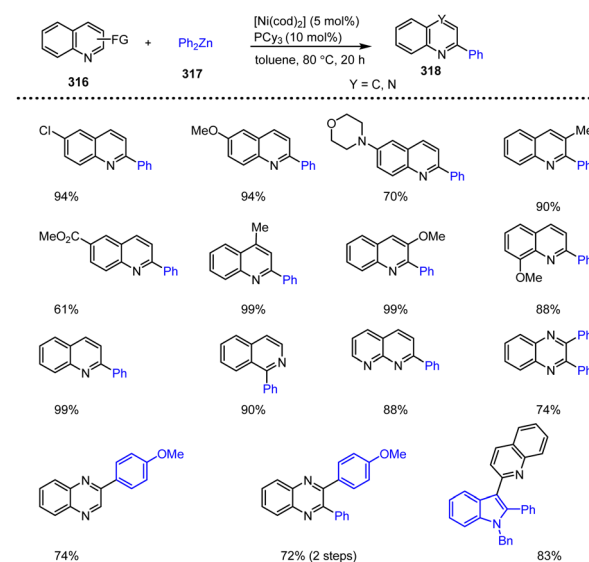
**Scheme 93** Pd-Catalyzed cross-coupling of 2-pyridyl organometallic reagents and heteroaryl chlorides with X-Phos ligand.

preparation of various heterocyclic aminoalkyl products **315** (Scheme 94), which are structural components of numerous biologically active compounds. The required aminoalkyl zinc bromides were readily obtained from the corresponding aminoalkyl chlorides by Mg insertion and transmetalation with ZnCl<sub>2</sub>. Suitable electrophilic coupling partners comprise aryl, heteroaryl and alkenyl iodides as well as the corresponding -bromides, -chlorides and -triflates. The viability of this method was impressively demonstrated by short total syntheses of the natural products (±)-galipinin and (±)-cusparin.<sup>194</sup>

Hyodo *et al.* have developed an oxidative atom-economic alternative to the traditional cross-coupling reactions between organohalides and organometallic species enabling a one-step arylation of electron-deficient N-heteroarenes. In this process, functionalized N-heterocycles **316**, such as quinolines, indoles and quinoxalines, were arylated at the most electrophilic site in the presence of a nickel catalyst and PCy<sub>3</sub> as ligand using diaryl zinc reagents **317** as shown in Scheme 95.<sup>195</sup>



**Scheme 94** Direct amino alkylation of heteroarenes via Ni-catalyzed Negishi cross-coupling reactions.



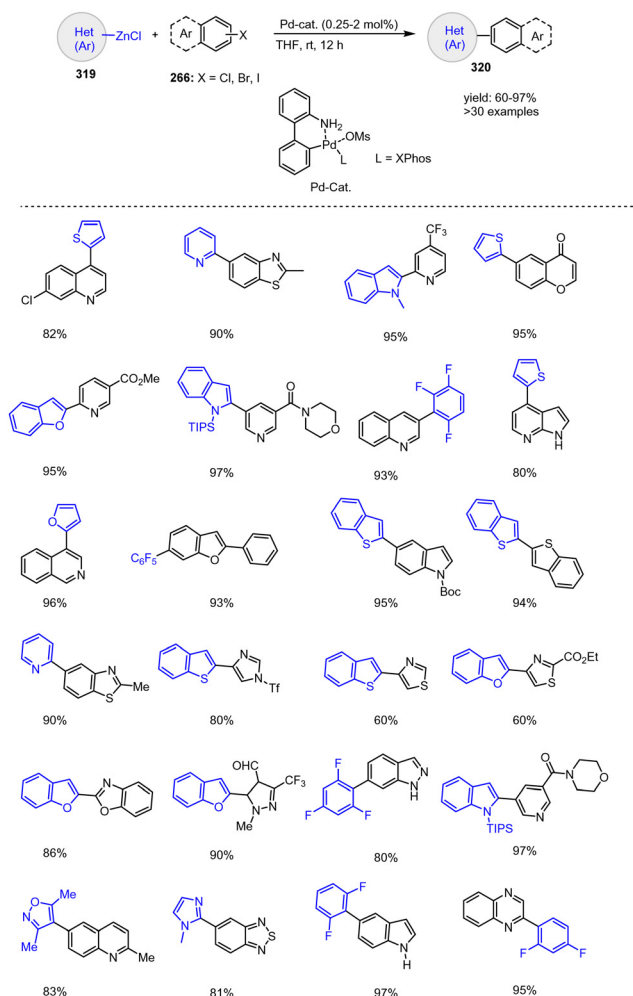
**Scheme 95** Ni-Catalyzed arylation of quinoline scaffolds using Ar<sub>2</sub>Zn reagents.

Buchwald and co-workers reported the Negishi cross-coupling of polyfunctionalized heteroaryl halides (Cl, Br, I) with 3,3-disubstituted allylzinc reagents using a previously established precatalytic palladacycle system with remarkable functional group tolerance. The method is characterized by an exceptionally low catalyst loading and mild reaction conditions. In addition, it enables the coupling of aryl/vinyl halides **266** with a wide range of complex heteroaromatic zinc compounds **319** that are often considered difficult. Many of the reported heterocyclic compounds **320** can be found as structural elements in pharmaceuticals (Scheme 96).<sup>196</sup> Moreover, Negishi couplings of 3,3-disubstituted allyl zinc reagents are of particular interest for the preparation of biologically active heteroaromatic compounds with prenyl-like side chains. A successful application of this method was demonstrated with the synthesis of the naturally occurring anti-HIV agent siamenol.

In 2013, Colombe *et al.* developed two protocols for the synthesis of solid and air-stable 2-pyridyl zinc reagents **322/323**, which were designed for bench-top handling and served as practical alternatives to organoboronates in cross-coupling



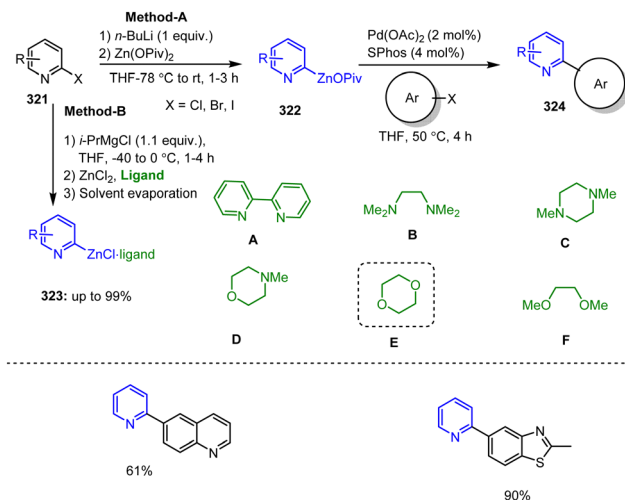




**Scheme 96** Pd-Catalyzed Negishi couplings of hetero(aryl) zinc reagents with heteroaryl halides.

reactions.<sup>197</sup> The organozinc reagents described were subsequently employed in Negishi couplings with aryl halides under Pd catalysis using SPhos as the ligand (Scheme 97). Moreover, the influence of additional stabilizing ligands on the manageability of the organozinc reagents **323** was investigated, with dioxane proving to be particularly suitable for enhancing stability under atmospheric conditions.

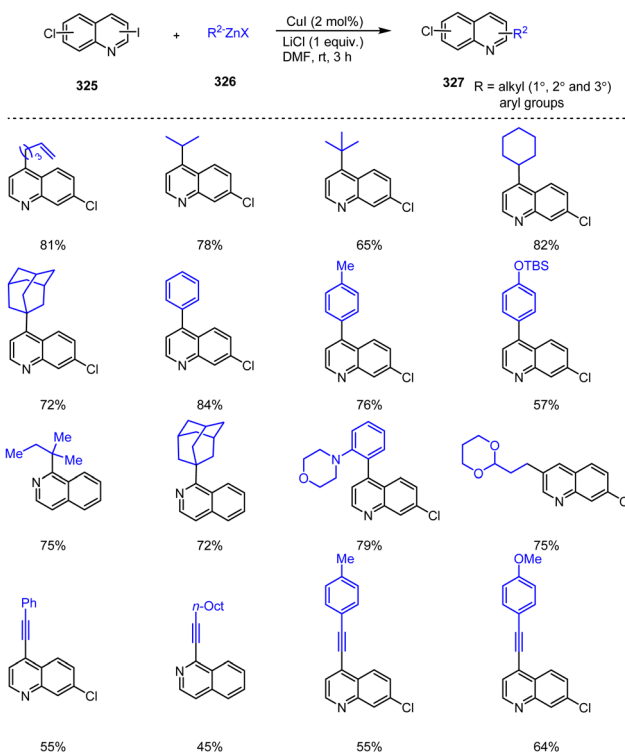
Giri and co-workers reported a strategy for the bisfunctionalization of non-activated olefins with two carbon-based units in the 1,2-position using substituted organozinc reagents. For this purpose, suitable alkyl/arylzinc reagents **326** were first prepared and reacted in radical cyclization reactions *in situ* with LiCl in DMF in the presence of CuI (2 mol%) to give C(sp<sup>3</sup>)-Cu complexes. The latter were then captured in a second tandem step by a ligand-free Cu-catalyzed Negishi cross-coupling reaction with aryl and heteroaryl iodides **326**. The resulting (arylmethyl)carbocycles and heterocycles **327** were obtained in moderate to high yields and allow the rapid construction of complex biologically active molecular fragments with *e.g.*, indanyl, dihydrofuranyl and indolyl rings



**Scheme 97** Preparation of solid 2-pyridyl zinc reagents for Negishi cross-couplings.

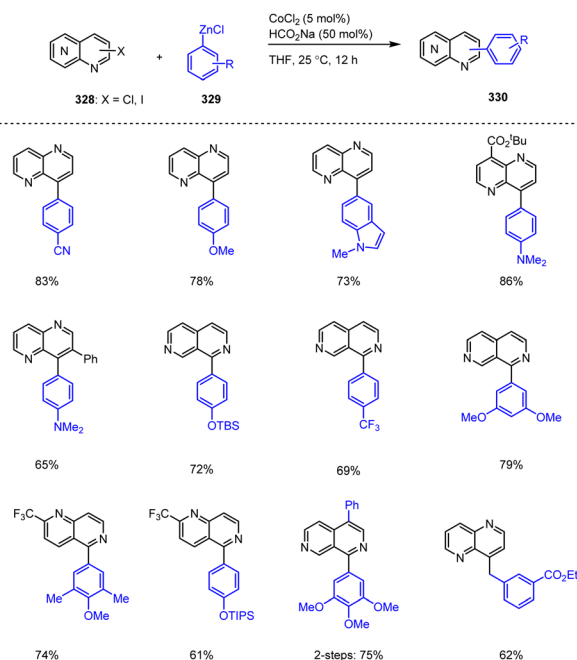
from simple and readily available chemical starting materials (Scheme 98).<sup>198</sup>

A report was published in 2017 by Greiner *et al.* on the preparation of polyfunctionalized naphthyridine derivatives **330** by Co-catalyzed Negishi cross-coupling reactions of halo-genated naphthyridines **328** with alkyl/aryl magnesium halides, as well as functionalized aryl/heteroaryl zinc reagents **329** in the presence of CoCl<sub>2</sub>·2LiCl (5 mol%) and sodium formate as an additive (50 mol%). Some of these naphthyridine derivatives



**Scheme 98** Cu-Catalyzed cross-coupling of aryl and alkyl zinc reagents with various heteroaryl iodides.



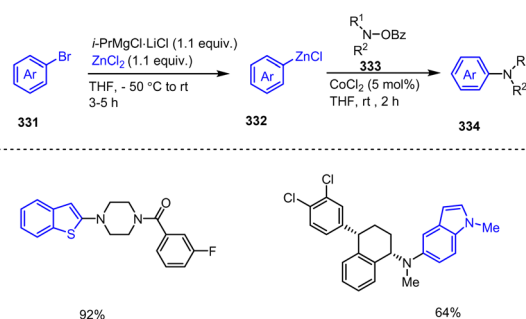


**Scheme 99** Co-Catalyzed arylation of aryl(heteroaryl) zinc reagents with iodo-/chloro-naphthyridines.

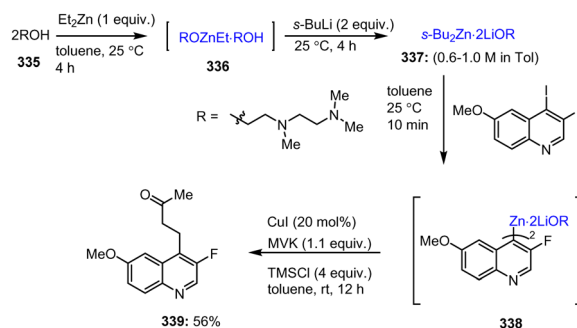
**330** are of interest for materials science applications due to their strong fluorescent properties (PLQE = 20–95%) with tuneable emissions from blue to yellow and long excited state lifetimes (3.8–12.0 ns, Scheme 99).<sup>199</sup>

Knochel and co-workers demonstrated that cobalt-catalyzed electrophilic aminations of heteroaryl zinc reagents **332** and aminating reagents ( $R^1R^2N-OBZ$ ) can proceed under moderate reaction conditions. This electrophilic process also enabled access to various C–N-coupled highly substituted amine products **334** in good to excellent yields using  $CoCl_2$  (5 mol%) in THF at room temperature (Scheme 100).<sup>200</sup> Furthermore, a candidate for a new anti-tuberculosis drug (Q203) was produced in a few steps and in very good yields with this method.<sup>183</sup>

Knochel, Hevia and co-workers developed a method for the preparation of polyfunctional diaryl and diheteroaryl zinc species by I/Zn or Br/Zn exchange reactions with bimetallic reagents of the general formula  $R'_2Zn \cdot 2LiOR$  ( $R' = s\text{-Bu}, t\text{-Bu}, p\text{-tol}$ ). With the help of these atom economic I/Zn and Br/Zn exchange reactions, even highly sensitive functional groups such as triazines, keto and aldehyde groups, as well as nitro groups could be tolerated in the substrate. Thus, this protocol allows access to many functionalized (hetero)arenes after scavenging reactions with different electrophiles. Scheme 101 shows an example of such a reaction sequence, in which alcohol **335** is first converted by  $Et_2Zn$  into the organozinc species **336**. Subsequent treatment with  $s\text{-BuLi}$  generates the reactive bimetallic reagent **337**, which then allows functionalization of the iodoquinoline backbone *via* nucleophile **338**, leading to the desired modified heteroaromatic compound **339** by Cu-catalyzed 1,4-addition to methyl vinyl ketone.



**Scheme 100** Amination of solid heteroaryl zinc pivalates with *O*-benzoylhydroxylamines.



**Scheme 101** Example for the preparation of a mixed-metal reagent and its application.

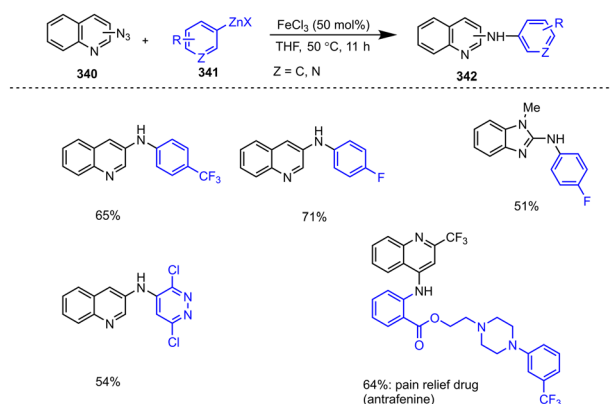
Structural and spectroscopic studies revealed the necessity of forming highly reactive bimetallic lithium bis(alkyl)bis(alkoxy) zincates to generate the polyfunctional aryl and heteroaryl zinc reagents from the corresponding organic iodides or bromides.<sup>201</sup>

Graßl *et al.* were able to show that a broad spectrum of alkyl, aryl and heteroaryl zinc halides can be successfully aminated with highly functionalized alkyl, aryl, and heterocyclic azides in the presence of  $FeCl_3$  (0.5 equiv.) and without further ligand addition. The reaction proceeded at 50 °C within 1 h in good yields and afforded highly functionalized secondary amines such as diarylamine **342** (Scheme 102).<sup>202</sup> This non-toxic Fe-mediated electrophilic amination protocol is particularly suitable for the synthesis of pharmaceutically active amine scaffolds and permits the successful use of peptidic azides.

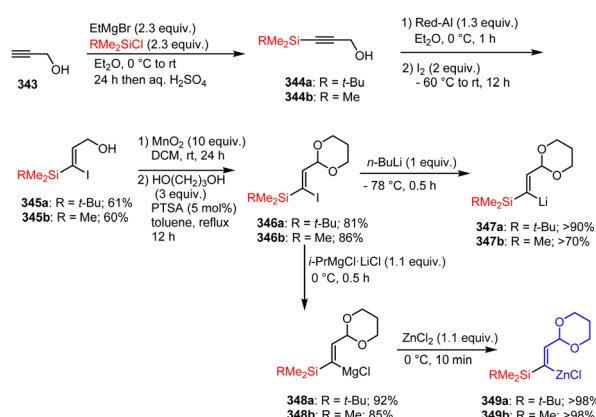
The Knochel group has developed an efficient approach to various polyfunctionalized 5-, 6- and 7-membered heterocycles, such as furans, pyrroles, quinolines, benzo[*b*]thieno[2,3-*b*]pyridines, naphthyridines, fused pyrazoles and 2,3-dihydrobenzo[*c*]azepines, using conjugated  $\beta$ -silylated organometallic reagents. The required conjugated alkenyl Li, Mg and Zn reagents **347–349** combine an electrophilic acetal function with two 1,1-bimetallic nucleophilic moieties of well-differentiated reactivity and are readily accessible from propargylic alcohols **343** (Scheme 103). In addition, the silyl group can be converted into various carbon–carbon bonds during the construction of the heterocycles.<sup>203</sup>

Examples of the preparation of fused 6-membered heterocycles such as quinolines, benzo[*b*]thieno[2,3-*b*]pyridine and



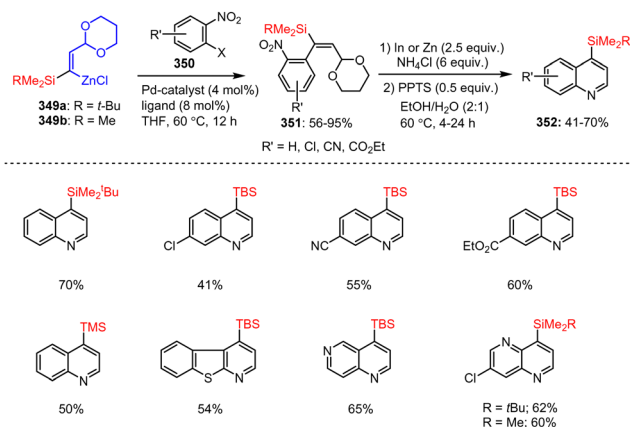


**Scheme 102** Fe-Mediated electrophilic amination of functionalized aryl zinc reagents with heteroaromatic azides.

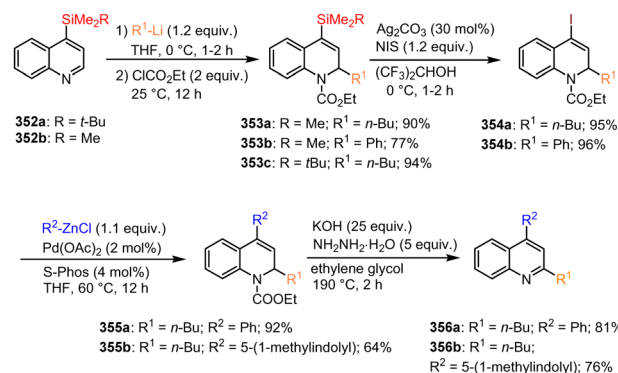


**Scheme 103** Preparation of acetal-protected organometallic Li-, Mg-, and Zn-reagents from propargylic alcohols.

naphthyridines relevant for pharmaceutical applications are depicted in Scheme 104. For this purpose, the alkenyl zinc compounds **349** were subjected to Pd-catalyzed Negishi cross-coupling reactions with various 1-halo-2-nitroarenes **350**,



**Scheme 104** Synthesis of fused hetero aromatic compounds via sequences of Pd-catalyzed cross-coupling, reduction, acidic hydrolysis, and cyclization.



**Scheme 105** Functionalization of the quinolines scaffolds via I/Si exchange, Negishi-coupling and subsequent re-aromatization.

yielding the corresponding alkenylated nitroarenes of type **351**. Subsequent In- or Zn-mediated reduction and acidic acetal cleavage afforded the desired condensed pyridines and quinoline **352** in 41–70% yields. The use of 3-bromo-2-nitrobenzo[*b*]thiophene or bromo-nitro-pyridines as coupling reagents thus enabled the rapid preparation of the valuable benzo[*b*]thieno[2,3-*b*]pyridines and the corresponding 1,5- and 1,6-naphthyridines.<sup>203</sup>

Further functionalization of the quinoline scaffolds through I/Si exchange proved to be extremely difficult for both the 4-TMS and the 4-TBS substituted derivatives **352a/b** due to the electron deficiency in the pyridyl ring. However, the 1,2-addition of an organolithium reagent (*n*BuLi or PhLi) to this pyridyl ring, followed by a scavenging reaction with ClCO<sub>2</sub>Et, led to its de-aromatization to form the alkenyl silane **353**. Subsequent iodination with NIS and Ag<sub>2</sub>CO<sub>3</sub> afforded the 4-iodo derivatives **354** in 95–96% yields, which were then successfully subjected to Negishi cross-coupling reactions with phenylzinc chloride or 1-methyl-1*H*-indol-5-yl-zinc bromide, leading to the coupling products **355**. Finally, re-aromatization with KOH/N<sub>2</sub>H<sub>4</sub> in ethylene glycol (190 °C, 2 h) afforded the desired 2,4-difunctionalized quinolines **356** (Scheme 105).<sup>203</sup>

Since the development of organozinc pivalates as versatile organometallic reagents with high reactivity and excellent air and moisture stability, these compounds have experienced an enormous surge in popularity for organic synthesis applications in recent years. The ease of handling and the absence of sophisticated inert gas techniques make these reagents widely applicable even in traditional (school) synthesis laboratories. In addition, novel protocols that guarantee increased tolerance even to highly sensitive functional groups facilitate the use of these reagents as tools for the construction of complex functional molecules in almost all areas of synthetic chemistry.

## 6 Selective examples of biologically active bicyclic fused hetero aromatic compounds

Many of the fused heterocyclic aromatic compounds presented so far in this review are fundamental scaffolds of biologically



**Table 1** Application of biologically active fused bicyclic heteroaromatic compounds and their scaffolds

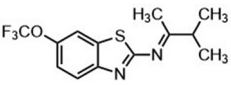
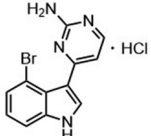
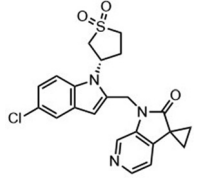
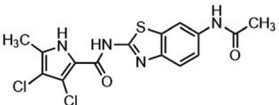
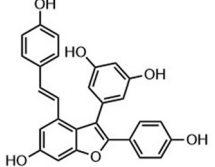
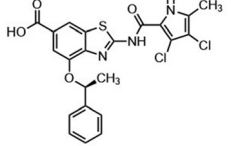
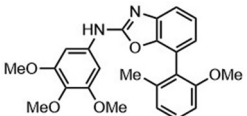
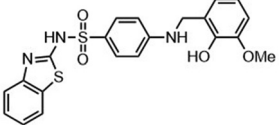
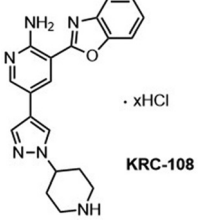
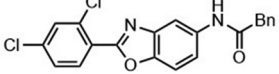
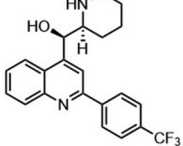
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1		Neuroprotective agent	204
2		Inhibitor of MRSA biofilms	205
3		Anti-RSV	206
4		Antibacterial	207
5		Antimicrobial	208
6		Inhibitor of bacterial enzyme	209
7		Inhibitor of RSK2	210
8		Inhibitor of 12-LOX	211
9		Antitumor activity	212
10		Inhibitor of SIRT3	213
11		Disruptor of biofilm formation in <i>V. cholerae</i> bacteria	214





Table 1 (continued)

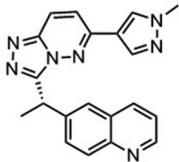
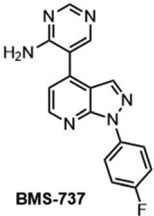
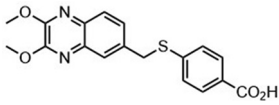
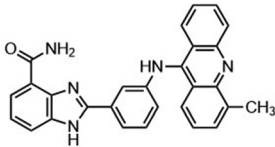
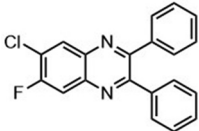
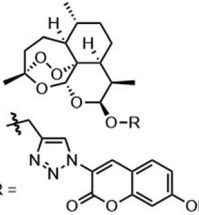
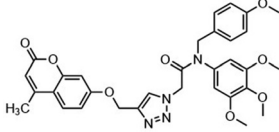
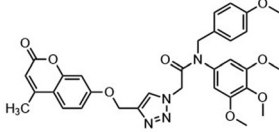
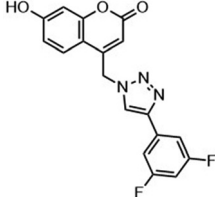
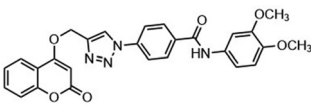
S. no.	Compound	Biological activity	Ref. no.
12	 <p><b>PF-04254644</b></p>	Inhibitor of pan-phosphodiesterase family	215
13	 <p><b>BMS-737</b></p>	Anti-castration resistant prostate cancer and CYP17 lyase-selective inhibitor	216
14		Antiviral	217
15		Inhibitor of Topo and PARP-1	218
16		Anti-HIV	219
17	 <p>R =</p>	Autofluorescent antimalarial	220
18		Anticancer	221
19		Anticancer	222
20		Anticancer	223
21		Anticancer	224



Table 1 (continued)

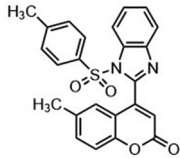
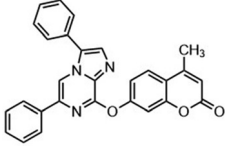
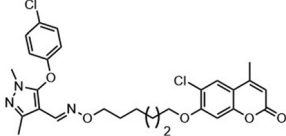
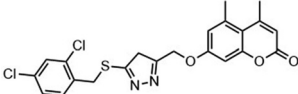
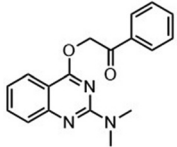
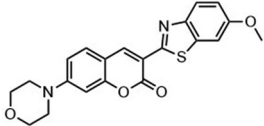
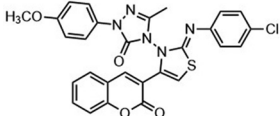
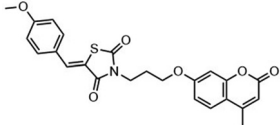
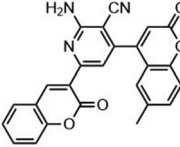
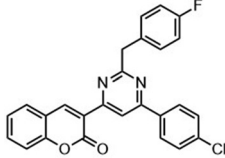
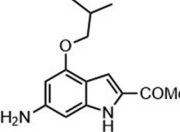
S. no.	Compound	Biological activity	Ref. no.
22		Anticancer	225
23		Anticancer	226
24		Antiproliferative	227
25		Anti-breast cancer	228
26		Anti-influenza virus activity	229
27		Potent inhibitor of ALK mutants	230
28		Anticancer	231
29		Anticancer	232
30		Anticancer	233
31		Anticancer	234
32		Telomerase inhibitor	235



Table 1 (continued)

S. no.	Compound	Biological activity	Ref. no.
33		Antiproliferative	236
34		Antifungal	237
35		Antiproliferative	238
36		Antitumor	239
37		Inhibitor of microtubule formation	240
38		Antimitotic activity	241
39		c-Met inhibitor	242
40		Leishmanicidal activity	243
41		Antioxidant	244
42		Anti-inflammatory	245
43		Antidepressant	246



Table 1 (continued)

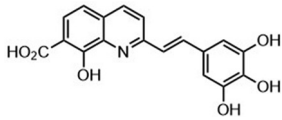
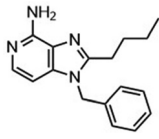
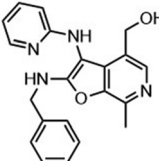
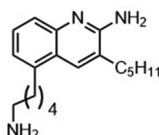
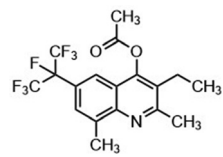
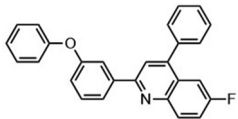
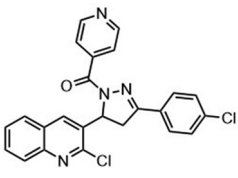
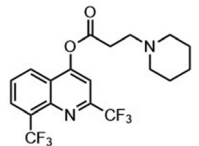
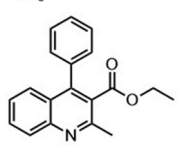
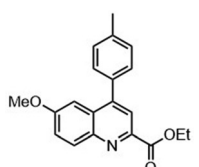
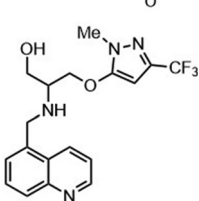
S. no.	Compound	Biological activity	Ref. no.
44		Anti-HIV	247
45		Human TLR7 agonist	248
46		Human TLR8 agonist	249
47		Human TLR8 agonist	250
48		Antifungal	251
49		Antibacterial	252
50		Antibacterial	253
51		Antifungal	254
52		Anti-tubercular	255
53		Anti-protozoal	256
54		Antimalarial	257





Table 1 (continued)

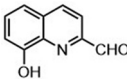
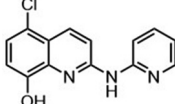
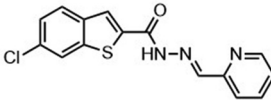
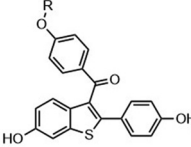
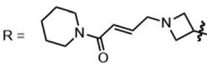
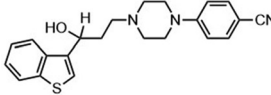
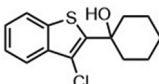
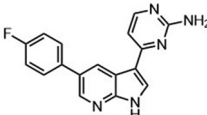
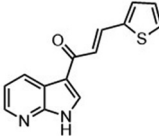
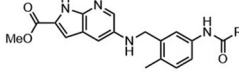
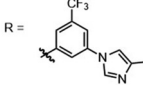
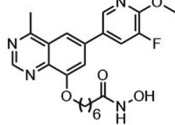
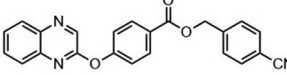
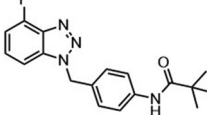
S. no.	Compound	Biological activity	Ref. no.
55		Anticancer	258
56		Anticancer	259
57		Antimicrobial agent	260
58	 R = 	Potent antagonist	261
59		Antidepressant	262
60		Bactericidal	263
61		Dual CDK2/CDK9 inhibitor and antitumor	264
62		CDK9 inhibitor	265
63	 R = 	Antiangiogenic and antitumor	266
64		PI3K HDAC inhibitor and antiproliferative	267
65		Fungicidal	268
66		Anti-enteroviral	269



Table 1 (continued)

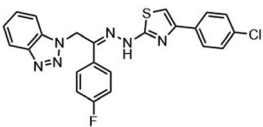
S. no.	Compound	Biological activity	Ref. no.
67		Antibacterial	270

Table 2 Selective examples of fused bicyclic heteroaromatic system and their scaffolds for material applications

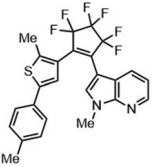
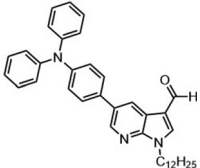
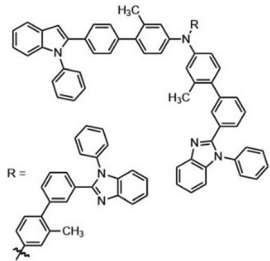
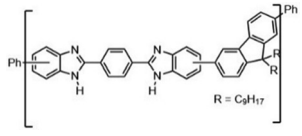
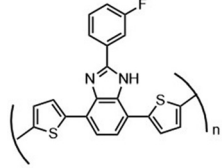
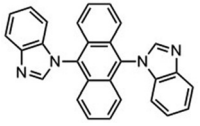
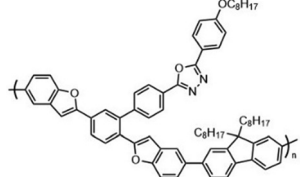
S. no.	Compound structure	Activity/properties	Ref. no.
1		Photochromo-phore	271
2		OLED	272
3		OLED	273
4		PLED	274
5		Electrochromic devices	275
6		LED	276
7		Optoelectronics	277



Table 2 (continued)

S. no.	Compound structure	Activity/properties	Ref. no.
8		Optoelectronics	278
9		White light emission	279
10		Fluorescent material	280
11		Organic electronics	281
12		Optoelectronics	282
13		Fluorescent sensor	283
14		Optoelectronics	284
15		Photovoltaics	285
16		Optoelectronics	286
17		OLEDs	287
18		Liquid crystalline semiconductors	288
19		Organic semiconductor	289
20		Electrochromic and optical properties	290



Table 2 (continued)

S. no.	Compound structure	Activity/properties	Ref. no.
21	<p>R = 2-hexyldecyl</p>	Field effect transistors	291
22		Optoelectronics	292
23		Solid state fluorescence	293
24		Chromophores	294
25		Chromophores	295
26		OLEDs	296
27		OLEDs	297
28		OLEDs	298
29		OLEDs	299
30		Fluorophores	300
31		Fluorescent material	301





Table 2 (continued)

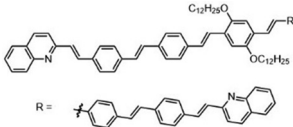
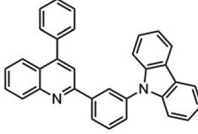
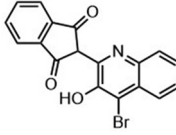
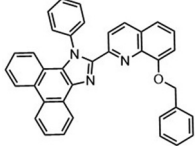
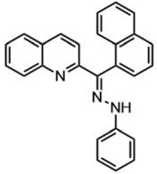
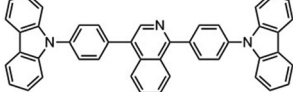
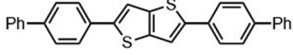
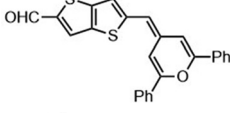
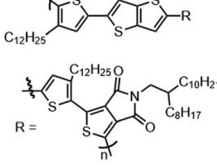
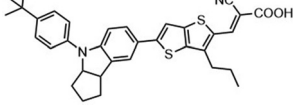
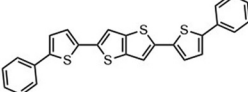
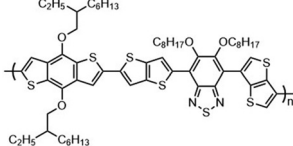
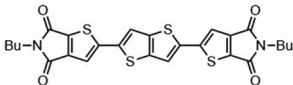
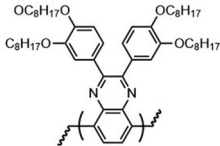
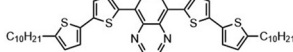
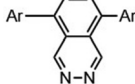
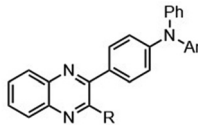
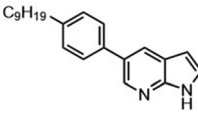
S. no.	Compound structure	Activity/properties	Ref. no.
32		Optoelectronics	302
33		OLEDs	303
34		Dye for bioimaging	304
35		Light emitting diodes	305
36		Photo-switches in photonics	306
37		OLEDs	307
38		Organic field effect transistors	308
39		Optical chromophores	309
40		Field effect transistors	310
41		Solar cells	311
42		P-type organic semi-conductors	312
43		Photovoltaics	313



Table 2 (continued)

S. no.	Compound structure	Activity/properties	Ref. no.
44		N-type molecular semi-conductors	314
45		Electric device applications	315
46		Organic field transistors	316
47		Photo-luminescence	317
48	 R = 9,9-diethylfluoren-2-yl; Ar=1-naphthyl	Electro-luminescent materials	318
49		OLEDs	319

active natural products and drugs. While several key heterocyclic structures can be isolated from natural sources or built up stepwise using classical synthetic routes, over the last three decades research groups have been increasingly engaged in the development of synthetic methods that allow rapid, modular access to these scaffolds. Highly functionalized condensed heteroaromatic compounds are characterized by diverse biological activities and are therefore of central importance as fundamental lead structures in various fields of medicinal chemistry and the pharmaceutical industry. For example, active substances for the treatment of malaria, tuberculosis, HIV, cancer, and depression, to name just a few applications, are based on different suitably functionalized heteroaromatic scaffolds. Synthetic methods that facilitate the construction of heteroaromatics and their modification through late-stage functionalization are therefore of great importance for the further development of drugs and for medical advances. The following section provides an overview of various condensed heteroaromatic motifs found in active ingredients, along with their pharmaceutical and biological applications.<sup>204–270</sup> (Table 1)

## 7 Selective examples for bicyclic heteroaromatic system-based material applications

Functionalized condensed heteroaromatic compounds are not only of interest due to their prevalence in biologically active compounds. Rather, highly  $\pi$ -conjugated sulfur-, oxygen- and

nitrogen-based fused heterocycles show great application potential for materials sciences and can be used for instance in the development of organic light-emitting diodes (OLEDs), polymer LEDs, organic semiconductors, field-effect transistors, photoelectrically luminescent materials and solar cells. Further potential areas of application can be derived from the table compiled in this section.<sup>271–319</sup> (Table 2)

## 8 Conclusions

This review highlights important synthetic advances in the functionalization of 5- or 6-membered ring-fused bicyclic heteroaromatic frameworks using organo-Li, Mg and Zn reagents. The syntheses presented include complex sequences based on direct selective metalations, halogen/metal exchange reactions, oxidative metal insertions and transmetalation processes. Protocols for efficient preparations of different functionalized organometallic reagents with aryl, heteroaryl, alkenyl, alkynyl and alkyl groups allow their use in high-performance transition metal-catalyzed cross-coupling reactions with various electrophiles, which makes such reaction sequences widely applicable in synthesis programs and for the development of active pharmaceutical ingredients. Thus, selective functionalization of important heterocyclic scaffolds such as quinoline, indole, benzofuran, benzothiophene, benzoxazole, benzothiazole, benzopyrimidine, anthranil, thienothiophene, coumarin, chromones, quinolones, phthalazines and their condensed heterocyclic scaffolds can now be carried out in almost any



desired position. This overview thus underlines the importance of modern synthetic technology with regard to functional group tolerance, cost efficiency and sustainable reaction conditions in the production of heterocyclic bioactive drugs and natural products.

## Data availability

The authors confirm that the data supporting the findings of this study are available in the article.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- V. Dhayalan, D. Sharma, R. Chatterjee and R. Dandela, *Eur. J. Org. Chem.*, 2023, e202300285.
- M. Balkenhohl and P. Knochel, *Chem. – Eur. J.*, 2020, **26**, 3688–3697.
- D. Tilly, F. Chevallier, F. Mongin and P. C. Gros, *Chem. Rev.*, 2014, **114**, 1207–1257.
- (a) O. M. Kuzmina, A. K. Steib, A. Moyeux, G. Cahiez and P. Knochel, *Synthesis*, 2015, 1696–1705; (b) A. Desaintjean, T. Haupt, L. J. Bole, N. R. Judge, E. Hevia and P. Knochel, *Angew. Chem., Int. Ed.*, 2021, **60**, 1513–1518.
- (a) P. Knochel, T. Thaler and C. Diene, *Isr. J. Chem.*, 2010, **50**, 547–557; (b) H. Ila, J. T. Markiewicz, V. Malakhov and P. Knochel, *Synthesis*, 2013, 2343–2371; (c) K. Schwärzer, H. Zipse, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 20235–20241.
- B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794–9824.
- R. P. Jumde, F. Lanza, T. Pellegrini and S. R. Harutyunyan, *Nat. Commun.*, 2017, **8**, 2058.
- M. Rodríguez-Fernández, X. Yan, J. F. Collados, P. B. White and S. R. Harutyunyan, *J. Am. Chem. Soc.*, 2017, **139**, 14224–14231.
- M. Fañanás-Mastral, M. Pérez, P. H. Bos, A. Rudolph, S. R. Harutyunyan and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2012, **51**, 1922–1925.
- S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824–2852.
- S. R. Harutyunyan, Z. Zhao, T. D. Hartog, K. Bouwmeester, A. J. Minnaard, B. L. Feringa and F. Govers, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 8507–8512.
- (a) M. A. Ganiek, M. R. Becker, M. Ketels and P. Knochel, *Org. Lett.*, 2016, **18**, 828–831; (b) L. Klier, E. Aranzamendi, D. Ziegler, J. Nickel, K. Karaghiosoff, T. Carell and P. Knochel, *Org. Lett.*, 2016, **18**, 1068–1071; (c) D. Haas, D. Sustac-Roman, S. Schwarz and P. Knochel, *Org. Lett.*, 2016, **18**, 6380–6383.
- J. Skotnitzki, L. Spessert and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 1509–1514.
- (a) J. Skotnitzki, A. Kremsmair, B. Kicin, R. Saeb, V. Ruf and P. Knochel, *Synthesis*, 2020, 873–881; (b) M. Ellwart, G. Höfner, A. Gerwien, K. T. Wanner and P. Knochel, *Synthesis*, 2017, 5159–5166.
- I. S. Makarov, C. E. Brocklehurst, K. Karaghiosoff, G. Koch and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 12774–12777.
- Y. B. Malysheva, S. Combes, A. Y. Fedorov, P. Knochel and A. E. Gavryushin, *Synlett*, 2012, 1205–1208.
- V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5516–5519.
- H. Langhals, P. Knochel, A. Walter and S. Zimdars, *Synthesis*, 2012, 3465–3476.
- T. Schlücker, V. Dhayalan, H. Langhals, C. Sämann and P. Knochel, *Asian J. Org. Chem.*, 2015, **4**, 763–769.
- (a) J. Nafe, S. Herbert, F. Auras, K. Karaghiosoff, T. Bein and P. Knochel, *Chem. – Eur. J.*, 2015, **21**, 1102–1107; (b) J. Nafe, F. Auras, K. Karaghiosoff, T. Bein and P. Knochel, *Org. Lett.*, 2015, **17**, 5356–5359.
- V. Dhayalan, F. R. Alcañiz, V. Werner, K. Karaghiosoff and P. Knochel, *Synthesis*, 2015, 3972–3982.
- S. Fernandez, M. A. Ganiek, M. Karpacheva, F. C. Hanusch, S. Reuter, T. Bein, F. Auras and P. Knochel, *Org. Lett.*, 2016, **18**, 3158–3161.
- S. I. Druzhinin, S. R. Dubbaka, P. Knochel, S. A. Kovalenko, P. Mayer, T. Senyushkina and K. A. Zachariasse, *J. Phys. Chem. A*, 2008, **112**, 2749–2761.
- (a) J. J. Patel, M. Laars, W. Gan, J. Board, M. O. Kitching and V. Snieckus, *Angew. Chem., Int. Ed.*, 2018, **57**, 9425–9429; (b) R. E. Miller, T. Rantanen, K. A. Ogilvie, U. Groth and V. Snieckus, *Org. Lett.*, 2010, **12**, 2198–2201; (c) D. Wu, A. Dasgupta, K.-H. Chen, M. Neuber-Hess, J. Patel, T. E. Hurst, J. D. Mewburn, P. D. A. Lima, E. Alizadeh, A. Martin, M. Wells, V. Snieckus and S. L. Archer, *FASEB J.*, 2020, **34**, 1447–1464.
- (a) M. A. J. Miah, M. P. Sibi, S. Chattopadhyay, O. B. Familoni and V. Snieckus, *Eur. J. Org. Chem.*, 2018, 440–446; (b) J. Fässler, J. A. McCubbin, A. Roglans, T. Kimachi, J. W. Hollett, R. W. Kunz, M. Tinkl, Y. Zhang, R. Wang, M. Campbell and V. Snieckus, *J. Org.*



- Chem.*, 2015, **80**, 3368–3386; (c) K. Groom, S. M. S. Hussain, J. Morin, C. Nilewski, T. Rantanen and V. Snieckus, *Org. Lett.*, 2014, **16**, 2378–2381; (d) X. Wang, J.-M. Fu and V. Snieckus, *Helv. Chim. Acta*, 2012, **95**, 2680–2694.
- 26 (a) B. Wei, Q. Ren, T. Bein and P. Knochel, *Angew. Chem., Int. Ed.*, 2021, **60**, 10409–10414; (b) P. Knochel and K. P. Cole, *Org. Process Res. Dev.*, 2021, **25**, 2188–2191; (c) S. H. Wunderlich and P. Knochel, *Angew. Chem., Int. Ed.*, 2009, **48**, 9717–9720.
- 27 (a) A. B. Bellan and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 1838–1841; (b) T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer and P. Knochel, *Nat. Chem.*, 2010, **2**, 125–130.
- 28 G. Berionni, V. Morozova, M. Heininger, P. Mayer, P. Knochel and H. Mayr, *J. Am. Chem. Soc.*, 2013, **135**, 6317–6324.
- 29 K. Groll, T. D. Blümke, A. Unsinn, D. Haas and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 11157–11161.
- 30 T. D. Blümke, T. Klatt, K. Koszinowski and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 9926–9930.
- 31 S. Somprasong, M. C. Reis and S. R. Harutyunyan, *Angew. Chem., Int. Ed.*, 2023, **62**, e202217328.
- 32 Y. Guo, M. Castiñeira Reis, J. Kootstra and S. R. Harutyunyan, *ACS Catal.*, 2021, **11**, 8476–8483.
- 33 (a) M. Zurro, L. Ge and S. R. Harutyunyan, *Org. Lett.*, 2022, **24**, 6686–6691; (b) Y. Guo and S. R. Harutyunyan, *Angew. Chem., Int. Ed.*, 2019, **58**, 12950–12954; (c) A. V. R. Madduri, A. J. Minnaard and S. R. Harutyunyan, *Org. Biomol. Chem.*, 2012, **10**, 2878–2884.
- 34 C. Boldrini, M. C. Reis and S. R. Harutyunyan, *J. Org. Chem.*, 2022, **87**, 12772–12782.
- 35 X. Yan and S. R. Harutyunyan, *Nat. Commun.*, 2019, **10**, 3402.
- 36 V. Fasano, R. C. Mykura, J. M. Fordham, J. J. Rogers, B. Banecki, A. Noble and V. K. Aggarwal, *Nat. Synth.*, 2022, **1**, 902–907.
- 37 K. J. Chambers, P. Sanghong, D. Carter Martos, G. Casoni, R. C. Mykura, D. Prasad Hari, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2023, **62**, e202312054.
- 38 H. Wang, W. Han, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207988.
- 39 (a) J. Wu, P. Lorenzo, S. Zhong, M. Ali, C. P. Butts, E. L. Myers and V. K. Aggarwal, *Nature*, 2017, **547**, 436–440; (b) D. P. Hari, R. Madhavachary, V. Fasano, J. Haire and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2021, **143**, 7462–7470.
- 40 (a) A. Fawcett, T. Biberger and V. K. Aggarwal, *Nat. Chem.*, 2019, **11**, 117–122; (b) D. P. Hari, J. C. Abell, V. Fasano and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2020, **142**, 5515–5520.
- 41 M. Giannerini, M. Fañanás-Mastral and B. L. Feringa, *Nat. Chem.*, 2013, **5**, 667–672.
- 42 M. Pérez, M. Fañanás-Mastral, P. H. Bos, A. Rudolph, S. R. Harutyunyan and B. L. Feringa, *Nat. Chem.*, 2011, **3**, 377–381.
- 43 (a) S. R. Harutyunyan, F. López, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 9103–9118; (b) C. Vila, M. Giannerini, V. Hornillos, M. Fañanás-Mastral and B. L. Feringa, *Chem. Sci.*, 2014, **5**, 1361–1367; (c) D. Heijnen, J.-B. Gualtierotti, V. Hornillos and B. L. Feringa, *Chem. – Eur. J.*, 2016, **22**, 3991–3995.
- 44 (a) B. Mao, K. Geurts, M. Fañanás-Mastral, A. W. van Zijl, S. P. Fletcher, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2011, **13**, 948–951; (b) P. H. Bos, A. Rudolph, M. Pérez, M. Fañanás-Mastral, S. R. Harutyunyan and B. L. Feringa, *Chem. Commun.*, 2012, **48**, 1748–1750.
- 45 Y. Cohen and I. Marek, *Acc. Chem. Res.*, 2022, **55**, 2848–2868.
- 46 Y. Cohen, A. Cohen and I. Marek, *Chem. Rev.*, 2021, **121**, 140–161.
- 47 D. S. Müller and I. Marek, *Chem. Soc. Rev.*, 2016, **45**, 4552–4566.
- 48 V. Lanke and I. Marek, *J. Am. Chem. Soc.*, 2020, **142**, 5543–5548.
- 49 F.-G. Zhang and I. Marek, *J. Am. Chem. Soc.*, 2017, **139**, 8364–8370.
- 50 (a) T. Pavličková, Y. Stöckl and I. Marek, *Org. Lett.*, 2022, **24**, 8901–8906; (b) C. Tugny, F.-G. Zhang and I. Marek, *Chem. – Eur. J.*, 2019, **25**, 205–209; (c) Y. Cohen and I. Marek, *Org. Lett.*, 2019, **21**, 9162–9165.
- 51 W. Erb, L. Kadari, K. Al-Mekhlafi, T. Roisnel, V. Dorcet, P. R. Krishna and F. Mongin, *Adv. Synth. Catal.*, 2020, **362**, 832–850.
- 52 (a) M. Hedidi, J. Maillard, W. Erb, F. Lassagne, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, T. Roisnel, V. Dorcet, M. Hamzé, Z. Fajloun, B. Baratte, S. Ruchaud, S. Bach, G. Bentabed-Ababsa and F. Mongin, *Eur. J. Org. Chem.*, 2017, 5903–5915; (b) M. Hedidi, G. Bentabed-Ababsa, A. Derdour, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, F. Chevallier, T. Roisnel, V. Dorcet and F. Mongin, *Tetrahedron*, 2016, **72**, 2196–2205.
- 53 M. Hedidi, D. Gandrath, Y. Kitazawa, Y. Tatsuya, M. Kimura, W. Erb, G. Bentabed-Ababsa, F. Chevallier, M. Uchiyama, P. Gros and F. Mongin, *New J. Chem.*, 2019, **43**, 14898–14907.
- 54 N. E. Behnke, K. Lovato, M. Yousufuddin and L. Kürti, *Angew. Chem., Int. Ed.*, 2019, **58**, 14219–14223.
- 55 P. V. Kattamuri, J. Yin, S. Siriwongsup, D.-H. Kwon, D. H. Ess, Q. Li, G. Li, M. Yousufuddin, P. F. Richardson, S. C. Sutton and L. Kürti, *J. Am. Chem. Soc.*, 2017, **139**, 11184–11196.
- 56 (a) Z. Zhou, Z. Ma, N. E. Behnke, H. Gao and L. Kürti, *J. Am. Chem. Soc.*, 2017, **139**, 115–118; (b) N. E. Behnke, R. Kielawa, D.-H. Kwon, D. H. Ess and L. Kürti, *Org. Lett.*, 2018, **20**, 8064–8068.
- 57 T. Verhelst, S. Verbeeck, O. Ryabtsova, S. Depraetere and B. U. W. Maes, *Org. Lett.*, 2011, **13**, 272–275.
- 58 P. Mampuy, T. D. Moseev, M. V. Varaksin, J. De Houwer, C. M. L. Vande Velde, O. N. Chupakhin, V. N. Charushin and B. U. W. Maes, *Org. Lett.*, 2019, **21**, 2699–2703.
- 59 O. Ryabtsova, T. Verhelst, M. Baeten, C. M. L. Vande Velde and B. U. W. Maes, *J. Org. Chem.*, 2009, **74**, 9440–9445.





- 60 (a) M. A. Oberli and S. L. Buchwald, *Org. Lett.*, 2012, **14**, 4606–4609; (b) H. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2017, **139**, 11590–11594; (c) W. Shu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 5355–5358; (d) W. Shu, L. Pellegatti, M. A. Oberli and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 10665–10669.
- 61 (a) K. T. O'Brien and A. B. Smith, III, *Org. Lett.*, 2019, **21**, 7655–7659; (b) Y. Chen, X. Zhang, F. Liu, G. He, J. Zhang, K. N. Houk, A. B. Smith and Y. Liang, *Chin. Chem. Lett.*, 2021, **32**, 441–444; (c) M. H. Nguyen and A. B. Smith, III, *Org. Lett.*, 2013, **15**, 4872–4875.
- 62 (a) X. Liu, J. Wang and J. Li, *Synlett*, 2022, 1688–1694; (b) Z. Duan, S. Dong and J. Li, *Org. Biomol. Chem.*, 2023, **21**, 5506–5510; (c) B. Hu, X. Cheng, Y. Hu, X. Liu, K. Karaghiosoff and J. Li, *Angew. Chem., Int. Ed.*, 2021, **60**, 15497–15502.
- 63 (a) A. N. Baumann, A. Music, J. Dechent, N. Müller, T. C. Jagau and D. Didier, *Chem. – Eur. J.*, 2020, **26**, 8382–8387; (b) F. Reiners, E. Joseph, B. Nißl and D. Didier, *Org. Lett.*, 2020, **22**, 8533–8537; (c) M. Eisold, A. Müller-Deku, F. Reiners and D. Didier, *Org. Lett.*, 2018, **20**, 4654–4658.
- 64 (a) J. L. Jeffrey and R. Sarpong, *Org. Lett.*, 2012, **14**, 5400–5403; (b) S. D. Robertson, M. Uzelac and R. E. Mulvey, *Chem. Rev.*, 2019, **119**, 8332–8405; (c) Y. Fu, B.-L. Gou, C.-Z. Shi, Z. Du and T. Shen, *ChemCatChem*, 2018, **10**, 4253–4257; (d) N. Tezuka, K. Shimojo, K. Hirano, S. Komagawa, K. Yoshida, C. Wang, K. Miyamoto, T. Saito, R. Takita and M. Uchiyama, *J. Am. Chem. Soc.*, 2016, **138**, 9166–9171; (e) S. Panda, A. Coffin, Q. N. Nguyen, D. J. Tantillo and J. M. Ready, *Angew. Chem., Int. Ed.*, 2016, **55**, 2205–2209; (f) Y. Nagashima, R. Takita, K. Yoshida, K. Hirano and M. Uchiyama, *J. Am. Chem. Soc.*, 2013, **135**, 18730–18733; (g) B. M. Trost and C. A. Kalnals, *Chem. – Eur. J.*, 2018, **24**, 9066–9074.
- 65 (a) R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, 2004, **104**, 2667–2722; (b) H. K. Khartabil, P. C. Gros, Y. Fort and M. F. Ruiz-López, *J. Am. Chem. Soc.*, 2010, **132**, 2410–2416; (c) G. Rouquet, D. C. Blakemore and S. V. Ley, *Chem. Commun.*, 2014, **50**, 8908–8911; (d) Y. Nassar, F. Rodier, V. Ferey and J. Cossy, *ACS Catal.*, 2021, **11**, 5736–5761.
- 66 (a) T. Blümke, Y.-H. Chen, Z. Peng and P. Knochel, *Nat. Chem.*, 2010, **2**, 313–318; (b) P. Knochel, M. A. Schade, S. Bernhardt, G. Manolikakes, A. Metzger, F. M. Piller, C. J. Rohbogner and M. Mosrin, *Beilstein J. Org. Chem.*, 2011, **7**, 1261–1277; (c) Z. Peng and P. Knochel, *Org. Lett.*, 2011, **13**, 3198–3201; (d) A. D. Benischke, G. Le Corre and P. Knochel, *Chem. – Eur. J.*, 2017, **23**, 778–782.
- 67 (a) C. Sämann, M. A. Schade, S. Yamada and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 9495–9499; (b) C. Sämann, V. Dhayalan, P. R. Schreiner and P. Knochel, *Org. Lett.*, 2014, **16**, 2418–2421; (c) V. Dhayalan and P. Knochel, *Synthesis*, 2015, 3246–3256; (d) V. Dhayalan, C. Sämann and P. Knochel, *Chem. Commun.*, 2015, **51**, 3239–3242; (e) D. Haas, J. M. Hammann, R. Greiner and P. Knochel, *ACS Catal.*, 2016, **6**, 1540–1552; (f) T. D. Blümke, T. Klatt, K. Koszinowski and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 9926–9930.
- 68 T. Brückl, I. Thoma, A. J. Wagner, P. Knochel and T. Carell, *Eur. J. Org. Chem.*, 2010, 6517–6519.
- 69 A. D. Benischke, L. Anthore-Dalion, G. Berionni and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 16390–16394.
- 70 M. Ketels, M. A. Ganiek, N. Weidmann and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 12770–12773.
- 71 D. S. Ziegler, B. Wei and P. Knochel, *Chem. – Eur. J.*, 2019, **25**, 2695–2703.
- 72 L. Anthore-Dalion, A. D. Benischke, B. Wei, G. Berionni and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 4046–4050.
- 73 M. Balkenhohl and P. Knochel, *SynOpen*, 2018, **02**, 0078–0095.
- 74 (a) N. M. Brikci-Nigassa, G. Bentabed-Ababsa, W. Erb and F. Mongin, *Synthesis*, 2018, 3615–3633; (b) S. M. Manolikakes, N. M. Barl, C. Sämann and P. Knochel, *Z. Naturforsch.*, 2013, **68b**, 411–422.
- 75 J. Board, J. L. Cosman, T. Rantanen, S. P. Singh and V. Snieckus, *Platin. Met. Rev.*, 2013, **57**, 234–258.
- 76 Y.-H. Chen, M. Ellwart, V. Malakhov and P. Knochel, *Synthesis*, 2017, 3215–3223.
- 77 F. H. Lutter, S. Graßl, L. Grokenberger, M. S. Hofmayer, Y.-H. Chen and P. Knochel, *ChemCatChem*, 2019, **11**, 5188–5197.
- 78 A. Kremsmair, J. H. Harenberg, K. Schwärzer, A. Hess and P. Knochel, *Chem. Sci.*, 2021, **12**, 6011–6019.
- 79 (a) A. B. Charette, C. Molinaro and C. Brochu, *J. Am. Chem. Soc.*, 2001, **123**, 12160–12167; (b) T. J. Greshock, K. P. Moore, R. T. McClain, A. Bellomo, C. K. Chung, S. D. Dreher, P. S. Kutchukian, Z. Peng, I. W. Davies, P. Vachal, M. Ellwart, S. M. Manolikakes, P. Knochel and P. G. Nantermet, *Angew. Chem., Int. Ed.*, 2016, **55**, 13714–13718; (c) Y.-H. Chen, C. P. Tüllmann, M. Ellwart and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 9236–9239.
- 80 W. A. Herrmann, A. M. J. Rost, J. K. M. Mitterpleininger, N. Szesni, S. Sturm, R. W. Fischer and F. E. Kühn, *Angew. Chem., Int. Ed.*, 2007, **46**, 7301–7303.
- 81 M. Ellwart and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 10662–10665.
- 82 A. Hernán-Gómez, E. Herd, E. Hevia, A. R. Kennedy, P. Knochel, K. Koszinowski, S. M. Manolikakes, R. E. Mulvey and C. Schnegelsberg, *Angew. Chem., Int. Ed.*, 2014, **53**, 2706–2710.
- 83 J. Li and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 11436–11440.
- 84 (a) V. Dhayalan, R. Dandela, K. B. Devi and R. Dhanu-suraman, *SynOpen*, 2022, **06**, 31–57; (b) B. Mao, M. Fañanás-Mastral and B. L. Feringa, *Chem. Rev.*, 2017, **117**, 10502–10566; (c) V. Dhayalan and M. Hayashi, *Synthesis*, 2012, 2209–2216; (d) C. A. Caputo and N. D. Jones, *Dalton Trans.*, 2007, 4627–4640, DOI: [10.1039/B709283K](https://doi.org/10.1039/B709283K).
- 85 (a) G. Yang and W. Zhang, *Chem. Soc. Rev.*, 2018, **47**, 1783–1810; (b) H.-L. Kwong, H.-L. Yeung, C.-T. Yeung,



- W.-S. Lee, C.-S. Lee and W.-L. Wong, *Coord. Chem. Rev.*, 2007, **251**, 2188–2222; (c) M. Hechavarría Fonseca and B. König, *Adv. Synth. Catal.*, 2003, **345**, 1173–1185; (d) A. Pfaltz, *Acc. Chem. Res.*, 1993, **26**, 339–345.
- 86 J. Rong, J. F. Collados, P. Ortiz, R. P. Jumde, E. Otten and S. R. Harutyunyan, *Nat. Commun.*, 2016, **7**, 13780.
- 87 U. Bhakta, P. V. Kattamuri, J. H. Siitonen, L. B. Alemany and L. Kürti, *Org. Lett.*, 2019, **21**, 9208–9211.
- 88 P. Ortiz, J. F. Collados, R. P. Jumde, E. Otten and S. R. Harutyunyan, *Angew. Chem., Int. Ed.*, 2017, **56**, 3041–3044.
- 89 (a) J. F. Collados, R. Solà, S. R. Harutyunyan and B. Macià, *ACS Catal.*, 2016, **6**, 1952–1970; (b) F. Caprioli, A. V. R. Madduri, A. J. Minnaard and S. R. Harutyunyan, *Chem. Commun.*, 2013, **49**, 5450–5452.
- 90 (a) J. Rong, T. Pellegrini and S. R. Harutyunyan, *Chem. – Eur. J.*, 2016, **22**, 3558–3570; (b) P. Ortiz, A. M. del Hoyo and S. R. Harutyunyan, *Eur. J. Org. Chem.*, 2015, 72–76; (c) Z. Wu, S. R. Harutyunyan and A. J. Minnaard, *Chem. – Eur. J.*, 2014, **20**, 14250–14255.
- 91 K. N. Venugopala, V. Rashmi and B. Odhav, *Biomed. Res. Int.*, 2013, **2013**, 963248.
- 92 P.-Y. Chung, Z.-X. Bian, H.-Y. Pun, D. Chan, A. S.-C. Chan, C.-H. Chui, J. C.-O. Tang and K.-H. Lam, *Future Med. Chem.*, 2015, **7**, 947–967.
- 93 (a) Salahuddin, M. Shaharyar and A. Mazumder, *Arab. J. Chem.*, 2017, **10**, S157–S173; (b) J. Farhat, L. Alzyoud, M. Alwahsh and B. Al-Omari, *Cancers*, 2022, **14**, 2196; (c) T. Van de Walle, L. Cools, S. Mangelinckx and M. D'Hooghe, *Eur. J. Med. Chem.*, 2021, **226**, 113865; (d) I. Briguglio, S. Piras, P. Corona, E. Gavini, M. Nieddu, G. Boatto and A. Carta, *Eur. J. Med. Chem.*, 2015, **97**, 612–648.
- 94 (a) B. S. Matada, R. Pattanashettar and N. G. Yernale, *Bioorg. Med. Chem.*, 2021, **32**, 115973; (b) S. Samanta, S. Kumar, E. K. Aratikatla, S. R. Ghorpade and V. Singh, *RSC Med. Chem.*, 2023, **14**, 644–657; (c) V. Yadav, J. Reang, V. Sharma, J. Majeed, P. C. Sharma, K. Sharma, N. Giri, A. Kumar and R. K. Tonk, *Chem. Biol. Drug Des.*, 2022, **100**, 389–418.
- 95 (a) D. Sharma, V. Dhayalan, R. Chatterjee, M. Khatravath and R. Dandela, *ChemistrySelect*, 2022, **7**, e202104299; (b) S. M. Umer, M. Solangi, K. M. Khan and R. S. Z. Saleem, *Molecules*, 2022, **27**, 7586; (c) M. E. Cinar and T. Ozturk, *Chem. Rev.*, 2015, **115**, 3036–3140; (d) C. Teixeira, N. Vale, B. Pérez, A. Gomes, J. R. B. Gomes and P. Gomes, *Chem. Rev.*, 2014, **114**, 11164–11220.
- 96 (a) N. Holmberg-Douglas and D. A. Nicewicz, *Chem. Rev.*, 2022, **122**, 1925–2016; (b) G. A. Ramann and B. J. Cowen, *Molecules*, 2016, **21**, 986; (c) T. Iwai and M. Sawamura, *ACS Catal.*, 2015, **5**, 5031–5040; (d) P. Kannaboina, K. Mondal, J. K. Laha and P. Das, *Chem. Commun.*, 2020, **56**, 11749–11762; (e) J. Wen and Z. Shi, *Acc. Chem. Res.*, 2021, **54**, 1723–1736.
- 97 (a) A. Corio, C. Gravier-Pelletier and P. Busca, *Molecules*, 2021, **26**, 5467; (b) M. Wasa, B. T. Worrell and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2010, **49**, 1275–1277; (c) A. K. Dhiman, A. Thakur, R. Kumar and U. Sharma, *Asian J. Org. Chem.*, 2020, **9**, 1502–1518; (d) M. Monika and S. Selvakumar, *Synthesis*, 2019, 4113–4136.
- 98 (a) D. Morgan, S. J. Yarwood and G. Barker, *Eur. J. Org. Chem.*, 2021, 1072–1102; (b) K. Urbina, D. Tresp, K. Sipps and M. Szostak, *Adv. Synth. Catal.*, 2021, **363**, 2723–2739; (c) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873–2920.
- 99 (a) G. Cahiez, A. Moyeux, J. Buendia and C. Duplais, *J. Am. Chem. Soc.*, 2007, **129**, 13788–13789; (b) E. J. Alexanian and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 15627–15635; (c) F. Rekhroukh, L. Estevez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune and D. Bourissou, *J. Am. Chem. Soc.*, 2016, **138**, 11920–11929; (d) Z.-Y. Wang, X.-S. Peng and H. N. C. Wong, *Asian J. Org. Chem.*, 2020, **9**, 1834–1840; (e) M. Karimzadeh-Younjali and O. F. Wendt, *Helv. Chim. Acta*, 2021, **104**, e2100114; (f) Y. Zhu, T. Xiong, W. Han and Y. Shi, *Org. Lett.*, 2014, **16**, 6144–6147.
- 100 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390–2392.
- 101 M. Jaric, B. A. Haag, A. Unsinn, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 5451–5455.
- 102 C. J. Rohbogner, S. Wirth and P. Knochel, *Org. Lett.*, 2010, **12**, 1984–1987.
- 103 C. J. Rohbogner, S. Wirth and P. Knochel, *Synfacts*, 2010, 0936.
- 104 S. Duez, A. K. Steib, S. M. Manolikakes and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 7686–7690.
- 105 K. Snégároff, T. T. Nguyen, N. Marquise, Y. S. Halauko, P. J. Harford, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, F. Chevallier, A. E. H. Wheatley, P. C. Gros and F. Mongin, *Chem. – Eur. J.*, 2011, **17**, 13284–13297.
- 106 M. Jaric, B. A. Haag, S. M. Manolikakes and P. Knochel, *Org. Lett.*, 2011, **13**, 2306–2309.
- 107 M. Balkenhohl, C. François, D. Sustac Roman, P. Quinio and P. Knochel, *Org. Lett.*, 2017, **19**, 536–539.
- 108 S. M. Manolikakes, M. Jaric, K. Karaghiosoff and P. Knochel, *Chem. Commun.*, 2013, **49**, 2124–2126.
- 109 S. Kumar Rout, A. Kastrati, H. Jangra, K. Schwärzer, A. S. Sunagatullina, M. Garny, F. Lima, C. E. Brocklehurst, K. Karaghiosoff, H. Zipse and P. Knochel, *Chem. – Eur. J.*, 2022, **28**, e202200733.
- 110 R. N. Rao and K. Chanda, *Bioorg. Chem.*, 2020, **99**, 103801.
- 111 C. Le Manach, D. González Cabrera, F. Douelle, A. T. Nchinda, Y. Younis, D. Taylor, L. Wiesner, K. L. White, E. Ryan, C. March, S. Duffy, V. M. Avery, D. Waterson, M. J. Witty, S. Wittlin, S. A. Charman, L. J. Street and K. Chibale, *J. Med. Chem.*, 2014, **57**, 2789–2798.
- 112 A. Unsinn and P. Knochel, *Chem. Commun.*, 2012, **48**, 2680–2682.
- 113 S. Duez, A. K. Steib and P. Knochel, *Org. Lett.*, 2012, **14**, 1951–1953.
- 114 A. Unsinn, S. H. Wunderlich and P. Knochel, *Adv. Synth. Catal.*, 2013, **355**, 989–995.



- 115 L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff and P. Knochel, *J. Am. Chem. Soc.*, 2012, **134**, 13584–13587.
- 116 C. I. Stathakis, S. M. Manolikakes and P. Knochel, *Org. Lett.*, 2013, **15**, 1302–1305.
- 117 J. M. Hammann, D. Haas and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 4478–4481.
- 118 T. Bresser, M. Mosrin, G. Monzon and P. Knochel, *J. Org. Chem.*, 2010, **75**, 4686–4695.
- 119 F. Crestey and P. Knochel, *Synthesis*, 2010, 1097–1106.
- 120 S. Zimdars, H. Langhals and P. Knochel, *Synthesis*, 2011, 1302–1308.
- 121 M. Balkenhohl, H. Jangra, I. S. Makarov, S.-M. Yang, H. Zipse and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 14992–14999.
- 122 M. Kienle, A. Unsinn and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 4751–4754.
- 123 T. Kunz and P. Knochel, *Chem. – Eur. J.*, 2011, **17**, 866–872.
- 124 G. Monzón, I. Tirota and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 10624–10627.
- 125 T. Kunz and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 1958–1961.
- 126 A. Frischmuth, A. Unsinn, K. Groll, H. Stadtmüller and P. Knochel, *Chem. – Eur. J.*, 2012, **18**, 10234–10238.
- 127 K. Groll, S. M. Manolikakes, X. M. du Jourdin, M. Jaric, A. Bredihhin, K. Karaghiosoff, T. Carell and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 6776–6780.
- 128 F. Crestey, S. Zimdars and P. Knochel, *Synthesis*, 2013, 3029–3037.
- 129 T. Klatt, D. S. Roman, T. León and P. Knochel, *Org. Lett.*, 2014, **16**, 1232–1235.
- 130 M. R. Becker and P. Knochel, *Angew. Chem., Int. Ed.*, 2015, **54**, 12501–12505.
- 131 J. Nafe, S. Herbert, F. Auras, K. Karaghiosoff, T. Bein and P. Knochel, *Chem. – Eur. J.*, 2015, **21**, 1102–1107.
- 132 S. Achelle, C. Baudequin and N. Plé, *Dyes Pigm.*, 2013, **98**, 575–600.
- 133 M. Balkenhohl, R. Greiner, I. S. Makarov, B. Heinz, K. Karaghiosoff, H. Zipse and P. Knochel, *Chem. – Eur. J.*, 2017, **23**, 13046–13050.
- 134 M. Balkenhohl, B. Salgues, T. Hirai, K. Karaghiosoff and P. Knochel, *Org. Lett.*, 2018, **20**, 3114–3118.
- 135 F. H. Lutter, L. Grokenberger, L. A. Perego, D. Broggini, S. Lemaire, S. Wagschal and P. Knochel, *Nat. Commun.*, 2020, **11**, 4443.
- 136 A. Hess, J. P. Prohaska, S. B. Doerrich, F. Trauner, F. H. Lutter, S. Lemaire, S. Wagschal, K. Karaghiosoff and P. Knochel, *Chem. Sci.*, 2021, **12**, 8424–8429.
- 137 K. Schwärzer, S. K. Rout, D. Bessinger, F. Lima, C. E. Brocklehurst, K. Karaghiosoff, T. Bein and P. Knochel, *Chem. Sci.*, 2021, **12**, 12993–13000.
- 138 S. Grosse, V. Mathieu, C. Pillard, S. Massip, M. Marchivie, C. Jarry, P. Bernard, R. Kiss and G. Guillaumet, *Eur. J. Med. Chem.*, 2014, **84**, 718–730.
- 139 L. Melzig, C. B. Rauhut, N. Naredi-Rainer and P. Knochel, *Chem. – Eur. J.*, 2011, **17**, 5362–5372.
- 140 E. Nagaradja, F. Chevallier, T. Roisnel, V. Dorcet, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis and F. Mongin, *Org. Biomol. Chem.*, 2014, **12**, 1475–1487.
- 141 M. Y. Messaoud, G. Bentabed-Ababsa, M. Hedidi, A. Derdour, F. Chevallier, Y. S. Halauko, O. A. Ivashkevich, V. E. Matulis, L. Picot, V. Thiéry, T. Roisnel, V. Dorcet and F. Mongin, *Beilstein J. Org. Chem.*, 2015, **11**, 1475–1485.
- 142 M. Hasyeoui, P. M. Chapple, F. Lassagne, T. Roisnel, M. Cordier, A. Samarat, Y. Sarazin and F. Mongin, *Eur. J. Org. Chem.*, 2023, e202300555.
- 143 M. F. Z. J. Amaral, A. A. Baumgartner, R. Vessecchi and G. C. Clososki, *Org. Lett.*, 2015, **17**, 238–241.
- 144 C. Schneider, E. Broda and V. Snieckus, *Org. Lett.*, 2011, **13**, 3588–3591.
- 145 D. Martinez-Solorio, B. Melillo, L. Sanchez, Y. Liang, E. Lam, K. N. Houk and A. B. Smith, III, *J. Am. Chem. Soc.*, 2016, **138**, 1836–1839.
- 146 M. E. Dalziel, J. J. Patel, M. K. Kaye, J. L. Cosman, M. O. Kitching and V. Snieckus, *Angew. Chem., Int. Ed.*, 2019, **58**, 7313–7317.
- 147 N. D. Adams, J. L. Adams, J. L. Burgess and A. M. Chaudhari, *et al.*, *J. Med. Chem.*, 2010, **53**, 3973–4001.
- 148 C. Schneider, E. David, A. A. Toutov and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 2722–2726.
- 149 G. Zhao, M. Alami and O. Provot, *RSC Adv.*, 2017, **7**, 46007–46013.
- 150 A. K. Steib, O. M. Kuzmina, S. Fernandez, S. Malhotra and P. Knochel, *Chem. – Eur. J.*, 2015, **21**, 1961–1965.
- 151 M. Balkenhohl, V. Valsamidou and P. Knochel, *Eur. J. Org. Chem.*, 2019, 5165–5168.
- 152 A. K. Steib, S. Fernandez, O. M. Kuzmina, M. Corpet, C. Gosmini and P. Knochel, *Synlett*, 2015, 1049–1054.
- 153 C. Sämann, B. Haag and P. Knochel, *Chem. – Eur. J.*, 2012, **18**, 16145–16152.
- 154 O. M. Kuzmina, A. K. Steib, D. Flubacher and P. Knochel, *Org. Lett.*, 2012, **14**, 4818–4821.
- 155 A. K. Steib, O. M. Kuzmina, S. Fernandez, D. Flubacher and P. Knochel, *J. Am. Chem. Soc.*, 2013, **135**, 15346–15349.
- 156 O. M. Kuzmina, A. K. Steib, J. T. Markiewicz, D. Flubacher and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 4945–4949.
- 157 A. Frischmuth and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 10084–10088.
- 158 N. M. Barl, E. Sansiaume-Dagousset, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **52**, 10093–10096.
- 159 Q. Chen, X. M. du Jourdin and P. Knochel, *J. Am. Chem. Soc.*, 2013, **135**, 4958–4961.
- 160 J. Nickel, M. Fernández, L. Klier and P. Knochel, *Chem. – Eur. J.*, 2016, **22**, 14397–14400.
- 161 M. Tsuda, K. Nozawa, K. Shimbo and J. I. Kobayashi, *J. Nat. Prod.*, 2003, **66**, 292–294.
- 162 R. Greiner, R. Blanc, C. Petermayer, K. Karaghiosoff and P. Knochel, *Synlett*, 2016, 231–236.
- 163 A. B. Bellan, O. M. Kuzmina, V. A. Vetsova and P. Knochel, *Synthesis*, 2017, 188–194.
- 164 D. S. Ziegler, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 6701–6704.





- 165 M. Balkenhohl, B. Heinz, T. Abegg and P. Knochel, *Org. Lett.*, 2018, **20**, 8057–8060.
- 166 P. R. Graves, J. J. Kwiek, P. Fadden, R. Ray, K. Hardeman, A. M. Coley, M. Foley and T. A. J. Haystead, *Mol. Pharmacol.*, 2002, **62**, 1364–1372.
- 167 J. Wei, H. Liang, C. Ni, R. Sheng and J. Hu, *Org. Lett.*, 2019, **21**, 937–940.
- 168 B. Heinz, D. Djukanovic, M. A. Ganiek, B. Martin, B. Schenkel and P. Knochel, *Org. Lett.*, 2020, **22**, 493–496.
- 169 A. T. Baviskar, C. Madaan, R. Preet, P. Mohapatra, V. Jain, A. Agarwal, S. K. Guchhait, C. N. Kundu, U. C. Banerjee and P. V. Bharatam, *J. Med. Chem.*, 2011, **54**, 5013–5030.
- 170 H. Gao, Q.-L. Xu, M. Yousufuddin, D. H. Ess and L. Kürti, *Angew. Chem., Int. Ed.*, 2014, **53**, 2701–2705.
- 171 S. Yamada, A. Gavryushin and P. Knochel, *Angew. Chem., Int. Ed.*, 2010, **49**, 2215–2218.
- 172 X. Yan, L. Ge, M. Castiñeira Reis and S. R. Harutyunyan, *J. Am. Chem. Soc.*, 2020, **142**, 20247–20256.
- 173 L. Zhu, X. Sheng, Y. Li, D. Lu, R. Qiu and N. Kambe, *Org. Lett.*, 2019, **21**, 6785–6789.
- 174 Z. Zhou, Z. Ma, N. E. Behnke, H. Gao and L. Kürti, *J. Am. Chem. Soc.*, 2017, **139**, 115–118.
- 175 R. P. Jumde, F. Lanza, M. J. Veenstra and S. R. Harutyunyan, *Science*, 2016, **352**, 433–437.
- 176 L. Ge, M. Zurro and S. R. Harutyunyan, *Chem. – Eur. J.*, 2020, **26**, 16277–16280.
- 177 A. Baralle, S. Otsuka, V. Guérin, K. Murakami, H. Yorimitsu and A. Osuka, *Synlett*, 2015, 327–330.
- 178 S. Bernhardt, G. Manolikakes, T. Kunz and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9205–9209.
- 179 C. I. Stathakis, S. Bernhardt, V. Quint and P. Knochel, *Angew. Chem., Int. Ed.*, 2012, **51**, 9428–9432.
- 180 N. M. Barl, V. Malakhov, C. Mathes, P. Lustenberger and P. Knochel, *Synthesis*, 2015, 692–700.
- 181 D. Haas, J. M. Hammann, F. H. Lutter and P. Knochel, *Angew. Chem., Int. Ed.*, 2016, **55**, 3809–3812.
- 182 J. M. Hammann, F. H. Lutter, D. Haas and P. Knochel, *Angew. Chem., Int. Ed.*, 2017, **56**, 1082–1086.
- 183 Y.-H. Chen, S. Graßl and P. Knochel, *Angew. Chem., Int. Ed.*, 2018, **57**, 1108–1111.
- 184 J. M. Hammann, L. Thomas, Y.-H. Chen, D. Haas and P. Knochel, *Org. Lett.*, 2017, **19**, 3847–3850.
- 185 M. S. Hofmayer, F. H. Lutter, L. Grokenberger, J. M. Hammann and P. Knochel, *Org. Lett.*, 2019, **21**, 36–39.
- 186 M. Leroux, T. Vorherr, I. Lewis, M. Schaefer, G. Koch, K. Karaghiosoff and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 8231–8234.
- 187 J. Li, E. Tan, N. Keller, Y.-H. Chen, P. M. Zehetmaier, A. C. Jakowetz, T. Bein and P. Knochel, *J. Am. Chem. Soc.*, 2019, **141**, 98–103.
- 188 (a) X. Cheng, X. Liu, S. Wang, Y. Hu, B. Hu, A. Lei and J. Li, *Nat. Commun.*, 2021, **12**, 4366; (b) J. Lin, K. Chen, J. Wang, J. Guo, S. Dai, Y. Hu and J. Li, *Chem. Sci.*, 2023, **14**, 8672–8680; (c) S. Dong, Z. Tian, J. Wang, L. He and J. Li, *J. Catal.*, 2023, **425**, 350–358.
- 189 J. Wang, Z. Duan, X. Liu, S. Dong, K. Chen and J. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202379.
- 190 A. Kremsmair, S. Graßl, C. J. B. Seifert, E. Godineau and P. Knochel, *Synthesis*, 2021, 4068–4074.
- 191 T. Čarný, T. Peňáška, S. Andrejčák and R. Šebesta, *Chem. – Eur. J.*, 2022, **28**, e202202040.
- 192 L. Melzig, A. Metzger and P. Knochel, *J. Org. Chem.*, 2010, **75**, 2131–2133.
- 193 M. R. Luzung, J. S. Patel and J. Yin, *J. Org. Chem.*, 2010, **75**, 8330–8332.
- 194 L. Melzig, T. Dennenwaldt, A. Gavryushin and P. Knochel, *J. Org. Chem.*, 2011, **76**, 8891–8906.
- 195 I. Hyodo, M. Tobisu and N. Chatani, *Chem. – Asian J.*, 2012, **7**, 1357–1365.
- 196 Y. Yang, N. J. Oldenhuis and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 615–619.
- 197 J. R. Colombe, S. Bernhardt, C. Stathakis, S. L. Buchwald and P. Knochel, *Org. Lett.*, 2013, **15**, 5754–5757.
- 198 S. Thapa, A. Kafle, S. K. Gurung, A. Montoya, P. Riedel and R. Giri, *Angew. Chem., Int. Ed.*, 2015, **54**, 8236–8240.
- 199 R. Greiner, D. S. Ziegler, D. Cibu, A. C. Jakowetz, F. Auras, T. Bein and P. Knochel, *Org. Lett.*, 2017, **19**, 6384–6387.
- 200 S. Graßl, Y.-H. Chen, C. Hamze, C. P. Tüllmann and P. Knochel, *Org. Lett.*, 2019, **21**, 494–497.
- 201 M. Balkenhohl, D. S. Ziegler, A. Desaintjean, L. J. Bole, A. R. Kennedy, E. Hevia and P. Knochel, *Angew. Chem., Int. Ed.*, 2019, **58**, 12898–12902.
- 202 S. Graßl, J. Singer and P. Knochel, *Angew. Chem., Int. Ed.*, 2020, **59**, 335–338.
- 203 Z.-L. Shen, V. Dhayalan, A. D. Benischke, R. Greiner, K. Karaghiosoff, P. Mayer and P. Knochel, *Angew. Chem., Int. Ed.*, 2016, **55**, 5332–5336.
- 204 M. Anzini, A. Chelini, A. Mancini, A. Cappelli, M. Frosini, L. Ricci, M. Valoti, J. Magistretti, L. Castelli, A. Giordani, F. Makovec and S. Vomero, *J. Med. Chem.*, 2010, **53**, 734–744.
- 205 W. M. Huggins, W. T. Barker, J. T. Baker, N. A. Hahn, R. J. Melander and C. Melander, *ACS Med. Chem. Lett.*, 2018, **9**, 702–707.
- 206 X. Zheng, C. Liang, L. Wang, K. Miao, B. Wang, W. Zhang, D. Chen, G. Wu, W. Zhu, L. Guo, S. Feng, L. Gao, H. C. Shen and H. Yun, *MedChemComm*, 2019, **10**, 970–973.
- 207 Ž. Skok, M. Barančoková, O. Benek, C. D. Cruz, P. Tammela, T. Tomašič, N. Zidar, L. P. Mašič, A. Zega, C. E. M. Stevenson, J. E. A. Mundy, D. M. Lawson, A. Maxwell, D. Kikelj and J. Ilaš, *ACS Med. Chem. Lett.*, 2020, **11**, 2433–2440.
- 208 G. Catinella, L. M. Mattio, L. Musso, S. Arioli, D. Mora, G. L. Beretta, N. Zaffaroni, A. Pinto and S. Dallavalle, *Int. J. Mol. Sci.*, 2020, **21**, 2168.
- 209 A. E. Cotman, M. Durcik, D. Benedetto Tiz, F. Fulgheri, D. Secci, M. Sterle, Š. Možina, Ž. Skok, N. Zidar, A. Zega, J. Ilaš, L. Peterlin Mašič, T. Tomašič, D. Hughes, D. L. Huseby, S. Cao, L. Garoff, T. Berruga Fernández, P. Giachou, L. Crone, I. Simoff, R. Svensson, B. Birnir, S. V. Korol, Z. Jin, F. Vicente, M. C. Ramos, M. De La Cruz,



- B. Glinghammar, L. Lenhammar, S. R. Henderson, J. E. A. Mundy, A. Maxwell, C. E. M. Stevenson, D. M. Lawson, G. V. Janssen, G. J. Sterk and D. Kikelj, *J. Med. Chem.*, 2023, **66**, 1380–1425.
- 210 A. Costales, M. Mathur, S. Ramurthy, J. Lan, S. Subramanian, R. Jain, G. Atallah, L. Setti, M. Lindvall, B. A. Appleton, E. Ornelas, P. Feucht, B. Warne, L. Doyle, S. E. Basham, I. Aronchik, A. B. Jefferson and C. M. Shafer, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 1592–1596.
- 211 D. K. Luci, J. B. Jameson, A. Yasgar, G. Diaz, N. Joshi, A. Kantz, K. Markham, S. Perry, N. Kuhn, J. Yeung, E. H. Kerns, L. Schultz, M. Holinstat, J. L. Nadler, D. A. Taylor-Fishwick, A. Jadhav, A. Simeonov, T. R. Holman and D. J. Maloney, *J. Med. Chem.*, 2014, **57**, 495–506.
- 212 S. Y. Han, C. O. Lee, S. H. Ahn, M. O. Lee, S. Y. Kang, H. J. Cha, S. Y. Cho, J. Du Ha, J. W. Ryu, H. Jung, H. R. Kim, J. S. Koh and J. Lee, *Invest. New Drugs*, 2012, **30**, 518–523.
- 213 H. S. Salo, T. Laitinen, A. Poso, E. Jarho and M. Lahtela-Kakkonen, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2990–2995.
- 214 B. León, J. C. N. Fong, K. C. Peach, W. R. Wong, F. H. Yildiz and R. G. Linington, *Org. Lett.*, 2013, **15**, 1234–1237.
- 215 J. J. Cui, H. Shen, M. Tran-Dubé, M. Nambu, M. McTigue, N. Grodsky, K. Ryan, S. Yamazaki, S. Aguirre, M. Parker, Q. Li, H. Zou and J. Christensen, *J. Med. Chem.*, 2013, **56**, 6651–6665.
- 216 C. Padmakar Darne, U. Velaparthi, M. Saulnier, D. Frennesson, P. Liu, A. Huang, J. Tokarski, A. Fura, T. Spires, J. Newitt, V. M. Spires, M. T. Obermeier, P. A. Elzinga, M. M. Gottardis, L. Jayaraman, G. D. Vite and A. Balog, *Bioorg. Med. Chem. Lett.*, 2022, **75**, 128951.
- 217 A. Carta, G. Sanna, I. Briguglio, S. Madeddu, G. Vitale, S. Piras, P. Corona, A. T. Peana, E. Laurini, M. Fermeiglia, S. Pricl, A. Serra, E. Carta, R. Loddo and G. Giliberti, *Eur. J. Med. Chem.*, 2018, **145**, 559–569.
- 218 Z. Yuan, S. Chen, C. Chen, J. Chen, C. Chen, Q. Dai, C. Gao and Y. Jiang, *Eur. J. Med. Chem.*, 2017, **138**, 1135–1146.
- 219 S. B. Patel, B. D. Patel, C. Pannecouque and H. G. Bhatt, *Eur. J. Med. Chem.*, 2016, **117**, 230–240.
- 220 L. Herrmann, M. Leidenberger, A. Sacramento de Moraes, C. Mai, A. Çapci, M. da Cruz Borges Silva, F. Plass, A. Kahnt, D. R. M. Moreira, B. Kappes and S. B. Tsogoeva, *Chem. Sci.*, 2023, **14**, 12941–12952.
- 221 D. J. Fu, P. Li, B. W. Wu, X. X. Cui, C. Bin Zhao and S. Y. Zhang, *Eur. J. Med. Chem.*, 2019, **165**, 309–322.
- 222 T. G. Kraljević, A. Harej, M. Sedić, S. K. Pavelić, V. Stepanić, D. Drenjančević, J. Talapko and S. Raić-Malić, *Eur. J. Med. Chem.*, 2016, **124**, 794–808.
- 223 R. An, Z. Hou, J. T. Li, H. N. Yu, Y. H. Mou and C. Guo, *Molecules*, 2018, **23**, 2281.
- 224 B. Kahveci, F. Yilmaz, E. Menteşe and S. Ülker, *Arch. Pharm. Chem. Life Sci.*, 2017, **350**, e1600369.
- 225 M. Holiyachi, S. L. Shastri, B. M. Chougala, L. A. Shastri, S. D. Joshi, S. R. Dixit, H. Nagarajaiah and V. A. Sunagar, *ChemistrySelect*, 2016, **1**, 4638–4644.
- 226 R. Goel, V. Luxami and K. Paul, *RSC Adv.*, 2015, **5**, 37887–37895.
- 227 H. Dai, M. Huang, J. Qian, J. Liu, C. Meng, Y. Li, G. Ming, T. Zhang, S. Wang, Y. Shi, Y. Yao, S. Ge, Y. Zhang and Y. Ling, *Eur. J. Med. Chem.*, 2019, **166**, 470–479.
- 228 S. Dhawan, N. Kerru, P. Awolade, A. Singh-Pillay, S. T. Saha, M. Kaur, S. B. Jonnalagadda and P. Singh, *Bioorg. Med. Chem.*, 2018, **26**, 5612–5623.
- 229 M. Wang, G. Zhang, Y. Wang, J. Wang, M. Zhu, S. Cen and Y. Wang, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127143.
- 230 S. Mah, J. Jang, D. Song, Y. Shin, M. Latif, Y. Jung and S. Hong, *Org. Biomol. Chem.*, 2019, **17**, 186–194.
- 231 S. K. J. Shaikh, M. S. Sannaikar, M. N. Kumbar, P. K. Bayannavar, R. R. Kamble, S. R. Inamdar and S. D. Joshi, *ChemistrySelect*, 2018, **3**, 4448–4462.
- 232 R. R. Manda, R. V. Nadh, T. L. Viveka, G. Angajala and V. Aruna, *J. Mol. Struct.*, 2023, **1285**, 135453.
- 233 B. M. Chougala, S. Samundeeswari, M. Holiyachi, N. S. Naik, L. A. Shastri, S. Dodamani, S. Jalalpure, S. R. Dixit, S. D. Joshi and V. A. Sunagar, *ChemistrySelect*, 2017, **2**, 5234–5242.
- 234 K. M. Hosamani, D. S. Reddy and H. C. Devarajegowda, *RSC Adv.*, 2015, **5**, 11261–11271.
- 235 S. Xue, L. Ma, R. Gao, Y. Li and Z. Li, *Acta Pharm. Sin. B*, 2014, **4**, 313–321.
- 236 D. S. Reddy, M. Kongot, V. Singh, M. A. Siddiquee, R. Patel, N. K. Singhal, F. Avecilla and A. Kumar, *Arch. Pharm.*, 2021, **354**, e2000181.
- 237 M. Mahapatra, P. Mohapatra, S. K. Sahoo, A. K. Bishoyi, R. N. Padhy and S. K. Paidesetty, *J. Mol. Struct.*, 2023, **1283**, 135190.
- 238 L. Yang, Z. Hu, J. Luo, C. Tang, S. Zhang, W. Ning, C. Dong, J. Huang, X. Liu and H. B. Zhou, *Bioorg. Med. Chem.*, 2017, **25**, 3531–3539.
- 239 M. T. Gabr, *Heterocycl. Commun.*, 2018, **24**, 243–247.
- 240 P. Mutai, G. Breuzard, A. Pagano, D. Allegro, V. Peyrot and K. Chibale, *Bioorg. Med. Chem.*, 2017, **25**, 1652–1665.
- 241 O. Galayev, Y. Garazd, M. Garazd and R. Lesyk, *Eur. J. Med. Chem.*, 2015, **105**, 171–181.
- 242 D. Lu, A. Shen, Y. Liu, X. Peng, W. Xing, J. Ai, M. Geng and Y. Hu, *Eur. J. Med. Chem.*, 2016, **115**, 191–200.
- 243 J. C. Coa, W. Castrillón, W. Cardona, M. Carda, V. Ospina, J. A. Muñoz, I. D. Vélez and S. M. Robledo, *Eur. J. Med. Chem.*, 2015, **101**, 746–753.
- 244 N. A. Liberto, J. B. Simões, S. de Paiva Silva, C. J. da Silva, L. V. Modolo, Â. de Fátima, L. M. Silva, M. Derita, S. Zacchino, O. M. P. Zuñiga, G. P. Romanelli and S. A. Fernandes, *Bioorg. Med. Chem.*, 2017, **25**, 1153–1162.
- 245 M. P. Pinz, A. S. Reis, R. L. de Oliveira, G. T. Voss, A. G. Vogt, M. do Sacramento, J. A. Roehrs, D. Alves, C. Luchese and E. A. Wilhelm, *Regul. Toxicol. Pharmacol.*, 2017, **90**, 72–77.
- 246 P. Zajdel, K. Marciniak, A. Maślankiewicz, K. Grychowska, G. Satała, B. Duszyńska, T. Lenda, A. Siwek, G. Nowak, A. Partyka, D. Wróbel, M. Jastrzębska-Więsek, A. J. Bojarski,





- A. Wesolowska and M. Pawlowski, *Eur. J. Med. Chem.*, 2013, **60**, 42–50.
- 247 J. F. Mouscadet and D. Desmaële, *Molecules*, 2010, **15**, 3048–3078.
- 248 E. Yoo, B. M. Crall, R. Balakrishna, S. S. Malladi, L. M. Fox, A. R. Hermanson and S. A. David, *Org. Biomol. Chem.*, 2013, **11**, 6526–6545.
- 249 D. B. Salunke, E. Yoo, N. M. Shukla, R. Balakrishna, S. S. Malladi, K. J. Serafin, V. W. Day, X. Wang and S. A. David, *J. Med. Chem.*, 2012, **55**, 8137–8151.
- 250 M. Beesu, G. Caruso, A. C. D. Salyer, K. K. Khetani, D. Sil, M. Weerasinghe, H. Tanji, U. Ohto, T. Shimizu and S. A. David, *J. Med. Chem.*, 2015, **58**, 7833–7849.
- 251 Y. M. Fang, R. R. Zhang, Z. H. Shen, H. K. Wu, C. X. Tan, J. Q. Weng, T. M. Xu and X. H. Liu, *J. Heterocycl. Chem.*, 2018, **55**, 240–245.
- 252 M. Alagumuthu and S. Arumugam, *Bioorg. Med. Chem.*, 2017, **25**, 1448–1455.
- 253 N. C. Desai, B. Y. Patel and B. P. Dave, *Med. Chem. Res.*, 2017, **26**, 109–119.
- 254 G. Z. Yang, J. K. Zhu, X. D. Yin, Y. F. Yan, Y. L. Wang, X. F. Shang, Y. Q. Liu, Z. M. Zhao, J. W. Peng and H. Liu, *J. Agric. Food Chem.*, 2019, **67**, 11340–11353.
- 255 B. Tanwar, A. Kumar, P. Yogeeswari, D. Sriram and A. K. Chakraborti, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5960–5966.
- 256 J. McNulty, R. Vemula, C. Bordón, R. Yolken and L. Jones-Brando, *Org. Biomol. Chem.*, 2014, **12**, 255–260.
- 257 S. Vandekerckhove, S. De Moor, D. Segers, C. De Kock, P. J. Smith, K. Chibale, N. De Kimpe and M. D'Hooghe, *MedChemComm*, 2013, **4**, 724–730.
- 258 S. H. Chan, C. H. Chui, S. W. Chan, S. H. L. Kok, D. Chan, M. Y. T. Tsoi, P. H. M. Leung, A. K. Y. Lam, A. S. C. Chan, K. H. Lam and J. C. O. Tang, *ACS Med. Chem. Lett.*, 2013, **4**, 170–174.
- 259 K. Li, Y. Li, D. Zhou, Y. Fan, H. Guo, T. Ma, J. Wen, D. Liu and L. Zhao, *Bioorg. Med. Chem.*, 2016, **24**, 1889–1897.
- 260 T. Barbier, A. Barbry, J. Magand, C. Badiou, F. Davy, A. Baudouin, Y. Queneau, O. Dumitrescu, G. Lina and L. Soullère, *Biomolecules*, 2022, **12**, 131.
- 261 C. Bai, S. Wu, S. Ren, M. Zhu, G. Luo and H. Xiang, *Bioorg. Med. Chem.*, 2021, **47**, 116395.
- 262 L. Berrade, B. Aisa, M. J. Ramirez, S. Galiano, S. Guccione, L. R. Moltzau, F. O. Levy, F. Nicoletti, G. Battaglia, G. Molinaro, I. Aldana, A. Monge and S. Perez-Silanes, *J. Med. Chem.*, 2011, **54**, 3086–3090.
- 263 P. J. Masih, T. Kesharwani, E. Rodriguez, M. A. Vertudez, M. L. Motakhaveri, T. K. Le, M. K. T. Tran, M. R. Cloyd, C. T. Kornman and A. M. Phillips, *Pharmaceuticals*, 2022, **15**, 39.
- 264 U. Singh, G. Chashoo, S. U. Khan, P. Mahajan, A. Nargotra, G. Mahajan, A. Singh, A. Sharma, M. J. Mintoo, S. K. Guru, H. Aruri, T. Thatikonda, P. Sahu, P. Chibber, V. Kumar, S. A. Mir, S. S. Bharate, S. Madishetti, U. Nandi, G. Singh, D. M. Mondhe, S. Bhushan, F. Malik, S. Mignani, R. A. Vishwakarma and P. P. Singh, *J. Med. Chem.*, 2017, **60**, 9470–9489.
- 265 M. A. Qhobosheane, L. J. Legoabe, B. Josselin, S. Bach, S. Ruchaud and R. M. Beteck, *Chem. Biol. Drug Des.*, 2020, **96**, 1395–1407.
- 266 B. Daydé-Cazals, B. Fauvel, M. Singer, C. Feneyrolles, B. Bestgen, F. Gassiot, A. Spenlinhauer, P. Warnault, N. Van Hijfte, N. Borjini, G. Chevé and A. Yasri, *J. Med. Chem.*, 2016, **59**, 3886–3905.
- 267 K. Zhang, F. Lai, S. Lin, M. Ji, J. Zhang, Y. Zhang, J. Jin, R. Fu, D. Wu, H. Tian, N. Xue, L. Sheng, X. Zou, Y. Li, X. Chen and H. Xu, *J. Med. Chem.*, 2019, **62**, 6992–7014.
- 268 X. Tang, Q. Zhou, W. Zhan, D. Hu, R. Zhou, N. Sun, S. Chen, W. Wu and W. Xue, *RSC Adv.*, 2022, **12**, 2399–2407.
- 269 R. Ibba, P. Corona, F. Nonne, P. Caria, G. Serreli, V. Palmas, F. Riu, S. Sestito, M. Nieddu, R. Loddo, G. Sanna, S. Piras and A. Carta, *Pharmaceuticals*, 2023, **16**, 429.
- 270 N. D. Gaikwad, S. V. Patil and V. D. Bobade, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3449–3454.
- 271 Z. Sun, H. Li, G. Liu, C. Fan and S. Pu, *Dyes Pigm.*, 2014, **106**, 94–104.
- 272 C. Martin, C. Borreguero, K. Kennes, M. Van Der Auweraer, J. Hofkens, G. De Miguel and E. M. García-Frutos, *ACS Energy Lett.*, 2017, **2**, 2653–2658.
- 273 Z. Ge, T. Hayakawa, S. Ando, M. Ueda, T. Akiike, H. Miyamoto, T. Kajita and M. A. Kakimoto, *Chem. Mater.*, 2008, **20**, 2532–2537.
- 274 H. Zhu, H. Tong, Y. Gong, S. Shao, C. Deng, W. Z. Yuan and Y. Zhang, *J. Polym. Sci., Part A: Polym. Chem.*, 2012, **50**, 2172–2181.
- 275 M. Ileri, S. O. Hacioglu and L. Toppare, *Electrochim. Acta*, 2013, **109**, 214–220.
- 276 S. Kumar, T. Marcato, S. I. Vasylevskyi, J. Jagielski, K. M. Fromm and C. J. Shih, *J. Mater. Chem. C*, 2019, **7**, 8938–8945.
- 277 S. Matsumura, A. R. Hlil, C. Lepiller, J. Gaudet, D. Guay, Z. Shi, S. Holdcroft and A. S. Hay, *J. Polym. Sci., Part A: Polym. Chem.*, 2008, **46**, 7207–7224.
- 278 A. P. Chafin, M. C. Davis, W. W. Lai, G. A. Lindsay, D. H. Park and W. N. Herman, *Opt. Mater.*, 2011, **33**, 1307–1315.
- 279 F. Lu, R. Hu, S. Wang, X. Guo and G. Yang, *RSC Adv.*, 2017, **7**, 4196–4202.
- 280 C. H. Chen, Z. H. Luo and K. Tan, *Macromol. Chem. Phys.*, 2018, **219**, 1–7.
- 281 G. K. Dutta, S. Guha and S. Patil, *Org. Electron.*, 2010, **11**, 1–9.
- 282 A. G. Dikundwar, G. K. Dutta, T. N. G. Row and S. Patil, *Cryst. Growth Des.*, 2011, **11**, 1615–1622.
- 283 G. R. Suman, S. G. Bubbly, S. B. Gudennavar and V. Gayathri, *J. Photochem. Photobiol., A*, 2019, **382**, 111947.
- 284 N. P. Thekkeppat, M. Lakshmipathi, A. S. Jalilov, P. Das, A. M. P. Peedikakkal and S. Ghosh, *Cryst. Growth Des.*, 2020, **20**, 3937–3943.
- 285 A. Iwan, M. Palewicz, M. Krompiec, M. Grucela-Zajac, E. Schab-Balcerzak and A. Sikora, *Spectrochim. Acta, Part A*, 2012, **97**, 546–555.



- 286 S. Pu, M. Li, C. Fan, G. Liu and L. Shen, *J. Mol. Struct.*, 2009, **919**, 100–111.
- 287 C. Seo, J. M. Choi, S. S. Hong, J. Y. Lee and S. Y. Seo, *Dyes Pigm.*, 2017, **136**, 145–149.
- 288 Y. J. Zhong, K. Q. Zhao, B. Q. Wang, P. Hu, H. Monobe, B. Heinrich and B. Donnio, *Dyes Pigm.*, 2020, **173**, 107964.
- 289 A. Tanimoto and T. Yamamoto, *Macromolecules*, 2006, **39**, 3546–3552.
- 290 E. Kaya, A. Balan, D. Baran, A. Cirpan and L. Toppare, *Org. Electron.*, 2011, **12**, 202–209.
- 291 S. Yum, T. K. An, X. Wang, W. Lee, M. A. Uddin, Y. J. Kim, T. L. Nguyen, S. Xu, S. Hwang, C. E. Park and H. Y. Woo, *Chem. Mater.*, 2014, **26**, 2147–2154.
- 292 Y. Chen, Q. Zhang, M. Du, G. Li, Z. Li, H. Huang, Y. Geng, X. Zhang and E. Zhou, *ACS Appl. Polym. Mater.*, 2019, **1**, 906–913.
- 293 C. Carayon and S. Fery-Forgues, *Photochem. Photobiol. Sci.*, 2017, **16**, 1020–1035.
- 294 T. Uchacz, P. Szlachcic, A. A. Fedorchuk, E. Gondek, A. Danel, B. Jarosz, A. M. ElNaggar, A. A. Albassam, I. V. Kityk, G. Lakshminarayana, P. Czaja and P. Karasiński, *J. Mol. Struct.*, 2018, **1173**, 531–540.
- 295 K. Erden and C. Dengiz, *J. Org. Chem.*, 2022, **87**, 4385–4399.
- 296 Z. Zhang, J. Xie, H. Wang, B. Shen, J. Zhang, J. Hao, J. Cao and Z. Wang, *Dyes Pigm.*, 2016, **125**, 299–308.
- 297 D. Y. Kim, J. Kang, S. E. Lee, Y. K. Kim and S. S. Yoon, *Luminescence*, 2017, **32**, 1180–1185.
- 298 B. Li, Z. Wang, S. J. Su, F. Guo, Y. Cao and Y. Zhang, *Adv. Opt. Mater.*, 2019, **7**, 1–8.
- 299 R. Keruckiene, S. Vekteryte, E. Urbonas, M. Guzauskas, E. Skuodis, D. Volyniuk and J. V. Grazulevicius, *Beilstein J. Org. Chem.*, 2020, **16**, 1142–1153.
- 300 Z. Wang, H. Li, Z. Peng, Z. Wang, Y. Wang and P. Lu, *RSC Adv.*, 2020, **10**, 30297–30303.
- 301 Z. Mao, L. Hu, X. Dong, C. Zhong, B. F. Liu and Z. Liu, *Anal. Chem.*, 2014, **86**, 6548–6554.
- 302 R. Flores-Noria, R. Vázquez, E. Arias, I. Moggio, M. Rodríguez, R. F. Ziolo, O. Rodríguez, D. R. Evans and C. Liebig, *New J. Chem.*, 2014, **38**, 974–984.
- 303 G. Sych, D. Volyniuk, O. Bezikonnyi, R. Lytvyn and J. V. Grazulevicius, *J. Phys. Chem. C*, 2019, **123**, 2386–2397.
- 304 P. Tarnow, C. Zordick, A. Bottke, B. Fischer, F. Kühne, T. Tralau and A. Luch, *Chem. Res. Toxicol.*, 2020, **33**, 742–750.
- 305 X. Shao, W. Liu, R. Guo, J. Chen and N. Zhou, *Dyes Pigm.*, 2021, **188**, 10919.
- 306 B. Mravec, Š. Budzák, M. Medved', L. F. Pašteka, C. Slavov, T. Saßmannshausen, J. Wachtveitl, J. Kožíšek, L. Hegedúsová, J. Filo and M. Cigáň, *J. Org. Chem.*, 2021, **86**, 11633–11646.
- 307 Q. Xie, Y. Qu, G. Wang, X. Luo, D. Zhang, H. Zhou, L. Wang, L. Wang, Y. Miao and J. Huang, *Dyes Pigm.*, 2022, **205**, 110559.
- 308 Y. Y. Noh, R. Azumi, M. Goto, B. J. Jung, E. Lim, H. K. Shim, Y. Yoshida, K. Yase and D. Y. Kim, *Chem. Mater.*, 2005, **17**, 3861–3870.
- 309 A. B. Marco, R. Andreu, S. Franco, J. Garín, J. Orduna, B. Villacampa and R. Alicante, *Tetrahedron*, 2013, **69**, 3919–3926.
- 310 Q. Wu, M. Wang, X. Qiao, Y. Xiong, Y. Huang, X. Gao and H. Li, *Macromolecules*, 2013, **46**, 3887–3894.
- 311 G. Li, M. Liang, H. Wang, Z. Sun, L. Wang, Z. Wang and S. Xue, *Chem. Mater.*, 2013, **25**, 1713–1722.
- 312 M. O. Ahmed, W. Pisula and S. G. Mhaisalkar, *Molecules*, 2012, **17**, 12163–12171.
- 313 X. Wang, Y. Sun, S. Chen, X. Guo, M. Zhang, X. Li, Y. Li and H. Wang, *Macromolecules*, 2012, **45**, 1208–1216.
- 314 M. Durso, D. Gentili, C. Bettini, A. Zanelli, M. Cavallini, F. De Angelis, M. Grazia Lobello, V. Biondo, M. Muccini, R. Capelli and M. Melucci, *Chem. Commun.*, 2013, **49**, 4298–4300.
- 315 M. Yasa, S. Surmeli, T. Depci, L. Toppare and S. O. Hacioglu, *Macromol. Chem. Phys.*, 2020, **221**, 1–10.
- 316 G. K. Dutta and S. Patil, *Org. Electron.*, 2012, **13**, 1266–1276.
- 317 F. S. Mancilha, B. A. DaSilveira Neto, A. S. Lopes, P. F. Moreira, F. H. Quina, R. S. Gonçalves and J. Dupont, *Eur. J. Org. Chem.*, 2006, 4924–4933.
- 318 K. R. Justin Thomas, M. Velusamy, T. Lin Jiann, C. H. Chuen and Y. T. Tao, *Chem. Mater.*, 2005, **17**, 1860–1866.
- 319 C. Martín, K. Kennes, M. Van der Auweraer, J. Hofkens, G. de Miguel and E. M. García-Frutos, *Adv. Funct. Mater.*, 2017, **27**, 1–10.

