ChemComm

FEATURE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, **53**, 1568

Received 1st December 2016,
Accepted 22nd December 2016

DOI: 10.1039/c6cc09550j

www.rsc.org/chemcomm

Synthesis of fully arylated (hetero)arenes

Shin Suzuki[a] and Junichiro Yamaguchi*[b]

Multiply arylated arenes are privileged structures with highly useful functions and fascinating optoelectronic and biological properties. This feature article reports the synthesis of fully arylated (hetero)arenes bearing more than two different aryl substituents and categorizes this emerging topic by the type of (hetero)arene core and the type of chemistry employed to install the (hetero)aryl substituents.

Introduction

Benzene, pyridine, thiophene, and other unsaturated ring structures are comprehensively called (hetero)arenes, which represent privileged structural motifs in functional molecules. In particular, structures that have many (hetero)arenes bonded together, *i.e.*, multiply arylated (hetero)arenes, have often been found in natural products, pharmaceuticals and functional organic materials (representative examples are shown in Fig. 1A).[1] For example, 1,3-bis-(*N*-carbazolyl)benzene (mCP: **1**) and diaryloxadiazole (PBD: **2**) have been often seen in the field of organic light-emitting diode (OLED) materials. Oligothiophene (DH-4T: **3**) has also displayed activity as a p-type semiconductor. Moreover, widely prescribed pharmaceuticals such as Arcoxia (etoricoxib: **4**) and Lipitor (atorvastatin: **5**) consist of three aromatic rings as their core, and natural products such as (−)-telomestatin (**6**) has a unique cyclic oligooxazole structure exhibiting telomerase inhibitor activity. Typically, such molecules have more than two different aryl substituents in order to tune their molecular function. In recent decades, many synthesis methods of multiply arylated (hetero)arenes have been reported.[2]

As a subclass of multiply arylated (hetero)arenes, fully arylated (hetero)arenes have also flourished as a unique structural class in functional organic materials and biologically active compounds

Shin Suzuki

Shin Suzuki was born in Mie, Japan, in 1990. He obtained a Masters degree in Chemistry from Nagoya University in 2015. Currently, he is a postgraduate student in the group of Kenichiro Itami at Nagoya University, and working with Junichiro Yamaguchi as his co-supervisor focusing on the programmed synthesis of multiply arylated aromatic molecules.

Junichiro Yamaguchi

Junichiro Yamaguchi was born in Tokyo, Japan, in 1979. He received his PhD in 2007 from the Tokyo University of Science under the supervision of Prof. Yujiro Hayashi. From 2007 to 2008, he was a postdoctoral fellow in the group of Prof. Phil S. Baran at The Scripps Research Institute (JSPS postdoctoral fellowship for research abroad). In 2008 he became an Assistant Professor at Nagoya University working with Prof. Kenichiro Itami and was promoted to Associate Professor in 2012. He then moved to Waseda University as an Associate Professor (principal investigator) in 2016. His research interests include the total synthesis of natural products and the innovation of synthetic methods.

---

[a] *Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan*
[b] *Department of Applied Chemistry, Waseda University, 3-4-1 Ohkubo, Shinjuku, Tokyo 169-8555, Japan. E-mail: junyamaguchi@waseda.jp*

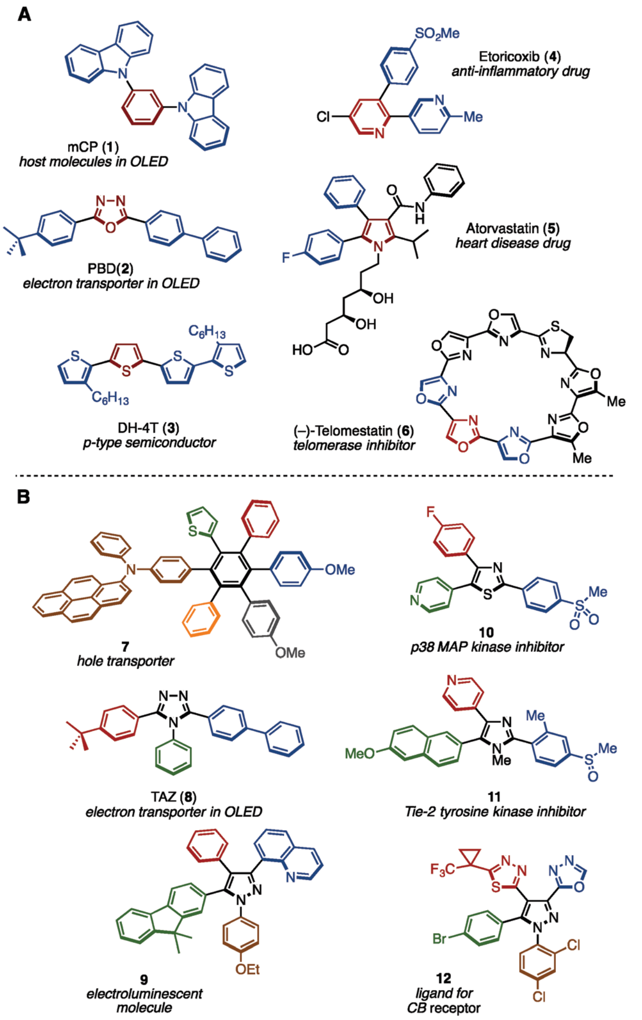


Fig. 1 (A) Widely used functional multiply arylated arenes and (B) examples of fully arylated arenes with different aryl groups.

(representative molecules are shown in Fig. 1B).[3] For example, hexaarylbenzene **7** functions as a hole transporter for solar cells. Triaryltriazole, TAZ (**8**), is known as an electron transporter in OLEDs, and tetraarylpyrazole **9** has been reported as an electroluminescent molecule. Triarylthiazole **10** as well as triarylimidazole **11** act as kinase inhibitors, and triarylpyrazole **12** has been reported as a ligand for the cannabinoid (CB) receptor. Despite the successful application of fully arylated (hetero)arenes with different aryl substituents, the synthesis of such (hetero)arenes has not been explored compared to partially arylated arenes due to the difficulty in synthesizing sterically hindered and highly unsymmetrical aromatic cores.

Despite these synthetic challenges, several compounds have already been utilized in the fields of materials science and biological science, indicating the possibility of fully arylated (hetero)arenes as widely used functional molecules. Therefore, general synthetic methods toward such molecules have recently been developed for the discovery of hitherto unknown functional molecules.

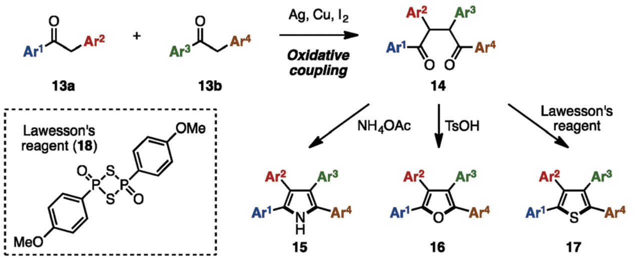
This article introduces recent efforts (made for the past fifteen years with the most emphasis on the past ten) toward fully (hetero)arylated (hetero)arenes bearing more than two different (hetero)aryl substituents, focusing on the synthetic methods used to generate such molecules. We categorized this emerging topic by the type of (hetero)arene core and the type of chemistry employed (mainly, cyclization, cross-coupling, and C–H arylation) to install the (hetero)aryl substituents.

Tetraarylpyrroles, furans, and thiophenes

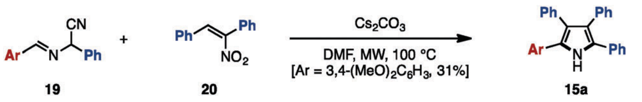
Cyclization

The Paal–Knorr synthesis is one of the most reliable methods to construct 5-membered aromatic compounds such as pyrroles, furans and thiophenes from 1,4-diketones.[4] Recently, using this classical approach, several research groups reported the synthesis of tetraarylpyrroles, tetraarylfurans, and tetraarylthiophenes with more than two different aryl groups (Scheme 1). To synthesize the 1,4-diketone precursor, common strategies involve the oxidative homocoupling (or heterocoupling) of deoxybenzoin derivatives **13** using $Cu(OAc)_2$[5a,d] or I_2[5b] as an oxidant or AgF[5c] as a catalyst to provide tetraarylated 1,4-diketones **14** with two or more different aryl groups. For example, in 2015, Wang and coworkers demonstrated the cross-coupling reaction of **13a** (*e.g.*, Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = *p*-MeC_6H_4) and **13b** (*e.g.*, Ar^3 = *p*-FC_6H_4, Ar^4 = C_6H_5) using a Ag catalytic system to synthesize 1,4-diketones **14** bearing four different aryl groups.[5c] The subsequent condensation of **14** with ammonium acetate gave the corresponding tetraarylpyrrole **15**. Treatment of **14** with *p*-toluenesulfonic acid (TsOH) or Lawesson's reagent (**18**) also provided tetraarylfurans **16** or tetraarylthiophenes **17**, respectively.

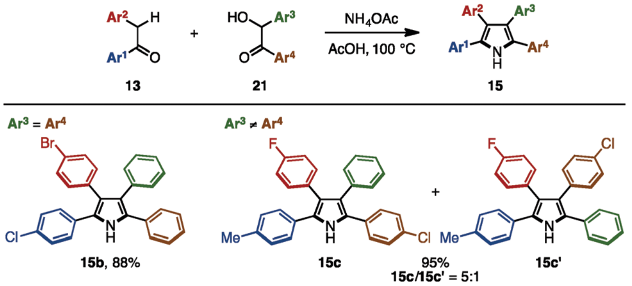
In 2007, Opatz and coworkers synthesized tetraarylpyrrole **15a** with two different aryl groups by a formal cycloaddition of α-(alkylideneamino)nitrile **19** and nitroolefin **20** with concomitant elimination of HCN and HNO_2, albeit in low yields (Scheme 2).[6] Although their protocol can potentially provide tetrasubstituted pyrroles with four different substituents, only one example was reported for tetraarylpyrroles.



Scheme 1 Paal–Knorr synthesis of pyrroles, furans and thiophenes.



Scheme 2 Cycloaddition from (alkylideneamino)nitriles and nitroolefins.



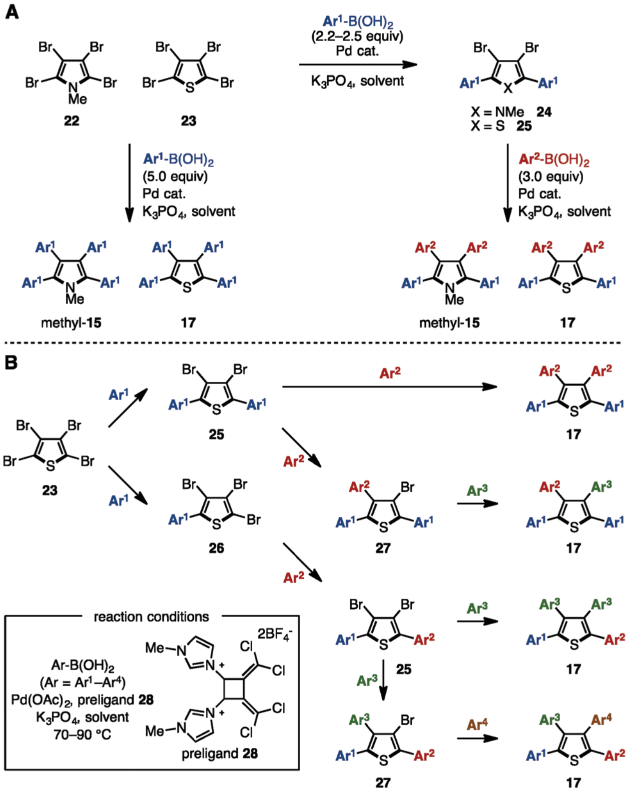
Scheme 3 Dehydrative synthesis of tetraarylpyrroles.

In 2016, Lei and coworkers reported a cross-dehydrative aromatization for the synthesis of tetraarylpyrroles **15** between deoxybenzoin **13** and benzoin derivatives **21** (Scheme 3).[7] A benzoin bearing the same aryl groups (**21b**: $Ar^3 = Ar^4$) reacted with **13** in the presence of ammonium acetate in acetic acid, giving tetraarylpyrroles such as **15b** with up to three different aryl groups as a single isomer. When benzoins with different aryl groups (**21c**: $Ar^3 \neq Ar^4$) were employed, tetraarylpyrroles with four different aryl groups were obtained with two regioisomers (**15c** and **15c′**) due to the tautomeric scrambling of the substituents on the benzoin.

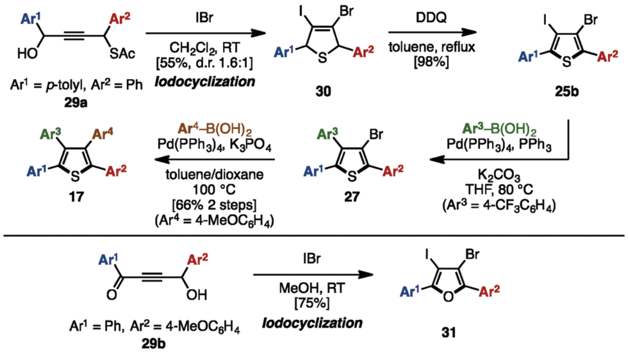
Cross-coupling

Transition-metal catalyzed cross-coupling reaction is one of the most reliable methods to install aryl groups onto aromatic molecules, in which the preparation of halogenated and metalated arenes is required prior to the cross-coupling step. Between 2007 and 2011, Langer and coworkers reported multiple cross-coupling reactions of *N*-methyltetrabromopyrrole (**22**) and tetrabromothiophene (**23**), giving *N*-methyltetraarylpyrroles and tetraarylthiophenes, respectively (Scheme 4A).[8] The treatment of **22** or **23** with 5.0 equivalents of arylboronic acid provided *N*-methyltetraarylpyrroles (methyl-**15**) and tetraarylthiophenes **17** with a single type of aryl group. By harnessing the different reactivities of the carbon–halogen bonds at the C2- and C3-positions on the pyrrole and thiophene, the synthesis of methyl-**15** and **17** bearing two different aryl groups was also achieved through sequential cross-coupling reactions.

In 2011, Schmidt and coworkers synthesized pre-ligand **28** and applied it in a Pd-catalyzed system to the sequential synthesis of arylated thiophenes **17** bearing up to four different aryl substituents (Scheme 4B).[9] Starting from tetrabromothiophene (**23**), nine different substitution patterns of arylated thiophenes were synthesized by Suzuki–Miyaura coupling under a single set of catalytic conditions (and only changing the reaction temperature and the number of equivalents of arylboronic acid when needed). Although differences in steric bulk must be present in Ar^1 (*p*-tolyl) and Ar^2 (*o*-tolyl) in order to introduce the Ar^3 group site-selectively (reaction from compound **25** to **17**), this protocol can provide tetraarylthiophenes with four different aryl groups.



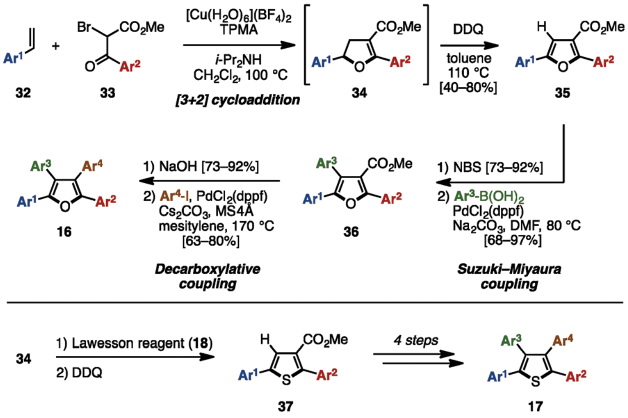
Scheme 4 (A) Suzuki–Miyaura cross-coupling of tetrabromopyrroles and thiophenes and (B) sequential Suzuki–Miyaura cross-coupling catalyzed by a Pd-imidazolium salt.



Scheme 5 Electrophilic iodocyclization of propargyl alcohols.

In 2011, Yamamoto and coworkers reported an electrophilic iodocyclization of propargyl alcohols for the synthesis of dihaloheterocycles (Scheme 5).[10] Treatment of propargyl alcohol **29a** with iodine monobromide (IBr) afforded 3-bromo-4-iododihydrothiophene **30**. After DDQ-mediated oxidation of **30**, subsequent iodo-selective Suzuki–Miyaura cross-coupling with an arylboronic acid furnished triarylthiophene **27**. Lastly, Suzuki–Miyaura coupling of **27** and another type of arylboronic acid gave tetraarylthiophene **17** with four different aryl groups. When 4-hydroxy-1,4-diaryl-but-2-yn-1-one **29b** was employed instead in this iodocyclization procedure, it furnished 3-bromo-4-iodo-2,5-diarylfuran **31**, which can be a precursor for tetraarylfurans with four different aryl substituents.

In 2015 and 2016, Nishikata and coworkers developed a Cu-catalyzed formal [3+2] cycloaddition for the synthesis of

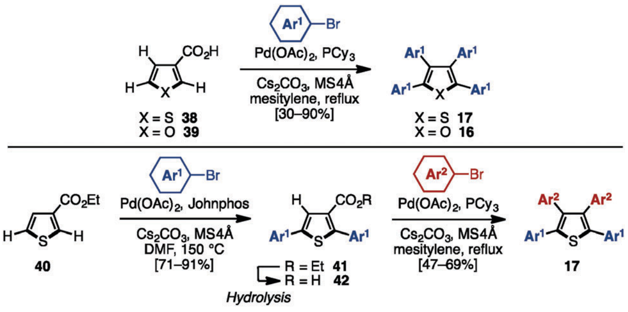


Scheme 6 Cu-catalyzed formal [3+2] cycloaddition.

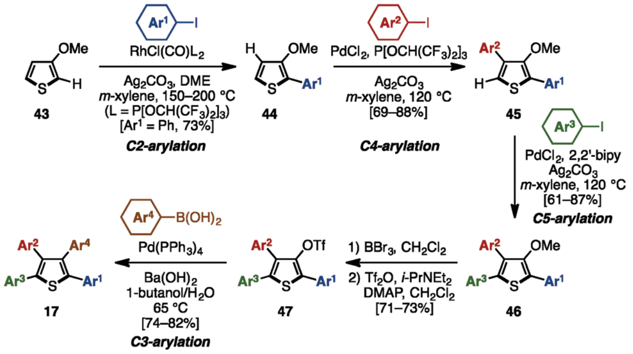
tetraarylfurans **16** and tetraarylthiophenes **17** with four different aryl groups (Scheme 6).[11] The [3+2] cycloaddition of styrene derivatives **32** with 2-bromo ketoesters **33** in the presence of a Cu salt, tris(2-pyridylmethyl)amine (TPMA) and diisopropylamine, proceeded, and the subsequent DDQ-mediated oxidation of cycloadduct **34** provided diarylated furans **35** in moderate to high yields as a single isomer. After bromination of **35**, Suzuki–Miyaura cross-coupling with arylboronic acids gave triarylfurans **36**. Hydrolysis of the methyl ester, followed by decarboxylative coupling with aryl iodides, afforded the corresponding tetraarylfurans **16**. In an alternative reaction pathway, intermediate **34** can be first treated with Lawesson's reagent and then oxidized to give thiophenes **37**, which could be converted to tetraarylthiophenes **17** in a similar manner.

C–H arylation

C–H arylation of (hetero)arenes not only enables the shortening of synthetic steps compared to typical cross-coupling reactions, but can also allow control of the position of aryl substituents at will.[12] In 2008, Miura and coworkers developed multiple arylation of 3-thiophene- (**38**) and 3-furancarboxylic acid (**39**), consisting of C–H arylation and decarboxylative arylation reactions (Scheme 7).[13] Treatment of **38** or **39** with excess aryl bromide in the presence of $\mathrm{Pd(OAc)_2}$ and $\mathrm{PCy_3}$ afforded tetraarylthiophenes **17** or tetraarylfurans **16** in moderate to high yields, although a small amount of triarylated isomer was also detected. When ethyl-3-thiophenecarboxylate (**40**) was selected as a substrate, 2,5-diarylation proceeded under Pd catalysis [$\mathrm{Pd(OAc)_2}$/Johnphos] to provide 2,5-diarylthiophenes **41** in high yields. After hydrolysis of the ester moiety of **41**, the resulting carboxylic acids **42** were subjected to a Pd-catalyzed C–H arylation and a decarboxylative arylation with aryl halides, providing tetraarylthiophenes **17** with two different aryl groups.



Scheme 7 Decarboxylative coupling of 3-thiophene- and 3-furancarboxylic acid.



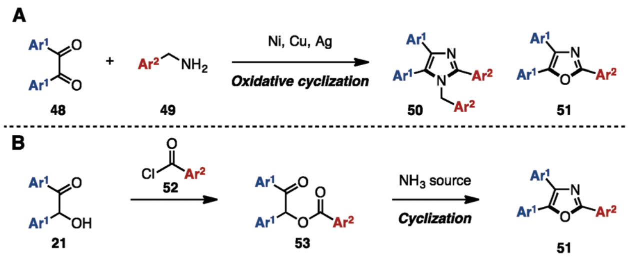
Scheme 8 Programmed synthesis of tetraarylthiophenes.

In 2009, Itami and coworkers demonstrated a programmed synthesis of tetraarylthiophenes **17** with four different aryl substituents by using a sequential regioselective C–H arylation strategy starting with 3-methoxythiophene (**43**: Scheme 8).[14] The synthesis commenced with C2-arylation of **43** with aryl iodides in the presence of $\mathrm{RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2}$,[15] giving 2-aryl-3-methoxythiophenes **44** with virtually complete regioselectivity. A C4-selective arylation of **44** with aryl iodides was catalyzed by $\mathrm{PdCl_2/P[OCH(CF_3)_2]_3}$ to afford 2,4-diaryl-3-methoxythiophenes **45** with high β-selectivity.[16] Treatment of **45** with aryl iodides using a $\mathrm{PdCl_2}$/2,2′-bipy catalyst then provided 2,4,5-triaryl-3-methoxythiophenes **46**.[16] After demethylation of **46**, followed by triflation of the resulting alcohol, triflates **47** were coupled with arylboronic acids in the presence of $\mathrm{Pd(PPh_3)_4}$ to produce tetraarylthiophenes **17** with virtually complete isomeric purities.

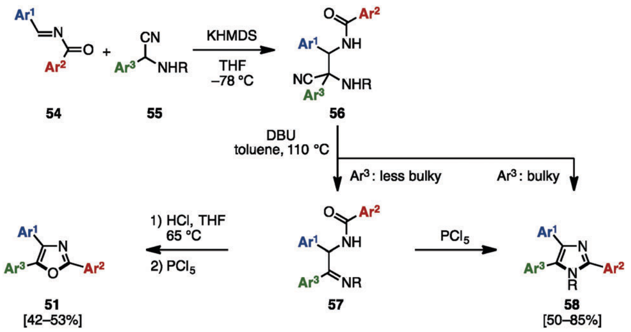
Triarylated 1,2-azoles and 1,3-azoles

Cyclization

Between 2013 and 2015, in order to synthesize *N*-arylmethyltriarylimidazoles **50** and triaryloxazoles **51**, several research groups reported an oxidative cyclization between benzil derivatives **48** and benzylamines **49** by using metal salts such as $\mathrm{NiCl_2{\cdot}6H_2O}$,[17a]



Scheme 9 Imidazole and oxazole synthesis from benzil and benzoin derivatives.



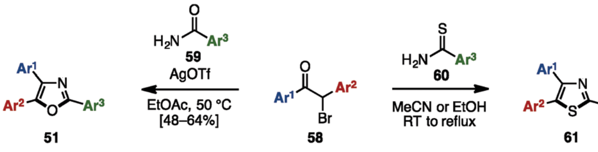
Scheme 10 Modular synthesis of triarylimidazoles and triaryloxazoles.

CuI,[17b,d] and Ag_2CO_3[17c] (Scheme 9A). In addition, triaryloxazoles **51** were synthesized by cyclization of benzoates **53** (which can be prepared by acylation of benzoins **21** with aroyl chlorides **52**) in the presence of a NH_3 source (Scheme 9B).[18]

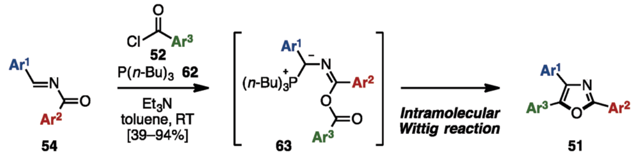
In 2008, Opatz and a coworker reported the modular synthesis of tetrasubstituted imidazoles and trisubstituted oxazoles by cross-coupling *N*-acylimines **54** and α-aminonitriles **55** (Scheme 10).[19] The synthesis began with a 1,2-addition of deprotonated α-aminonitriles **56** onto *N*-acylimines **54**, affording the corresponding adducts **56**. Treatment of **56** with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) under refluxing toluene furnished α-acylaminoimines **57**, which can spontaneously cyclize to imidazoles **58** depending on the substitution pattern at the C5 position (Ar^3). Bulky substituents at the C5 position promoted the spontaneous cyclization to form **58**, but in other cases, **57** could be converted to imidazoles **58** by treatment with PCl_5. Hydrolysis of imines **57** under acidic conditions provided the corresponding ketones, which were dehydrated with PCl_5 to afford triaryloxazoles **51** with three different aryl groups.

The Bredereck synthesis is one of the fundamental methods to construct substituted oxazoles and thiazoles.[20] Using this approach, in 2014, Bailey and a coworker reported a silver-promoted oxazole synthesis with α-bromoketones **58** and aryl amides **59**, giving triaryloxazoles **51** in moderate yields (Scheme 11).[21] Cyclization with aryl thioamide **60** instead of **59** smoothly proceeded even in the absence of silver salt to form triarylthiazoles **61**.

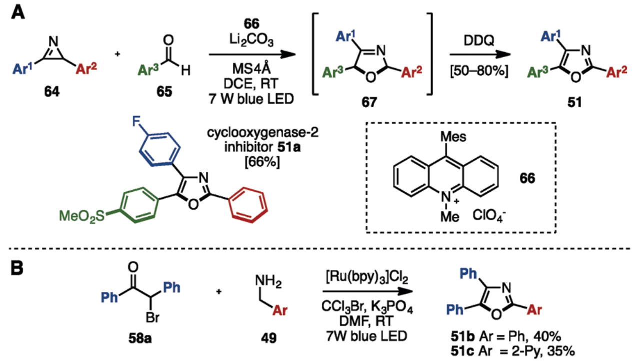
In 2014, Lin and coworkers applied an intramolecular Wittig-type reaction for the synthesis of trisubstituted oxazoles from *N*-acylimines **54** (Scheme 12).[22] Treatment of **54** with acyl chlorides **52** in the presence of $P(n\text{-}Bu)_3$ (**62**) and Et_3N provided triaryloxazoles **51** with three different aryl groups in moderate to excellent yields. The mechanism of this reaction was proposed to be an intramolecular Wittig-type reaction of presumable phosphorus ylides **63**, which were formed by 1,4-addition of $P(n\text{-}Bu)_3$ (**62**) to **54** and *O*-acylation with **52**.



Scheme 11 Bredereck synthesis of oxazoles and thiazoles.



Scheme 12 Triaryloxazole synthesis *via* the intramolecular Wittig reaction.



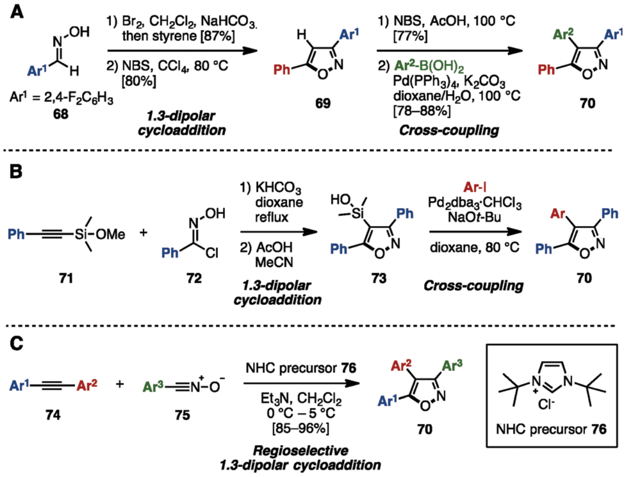
Scheme 13 Triaryloxazole synthesis enabled by photoredox catalysis.

Recently, visible-light photoredox catalysis has attracted significant attention as a green and sustainable synthetic method to make substituted heterocycles under mild reaction conditions.[23] In 2015, Xiao and coworkers disclosed the synthesis of trisubstituted oxazoles including triaryloxazoles from 2*H*-azirines **64** and aryl aldehydes **65** by using 9-mesityl-10-methylacridinium perchlorate **66** as the photoredox catalyst (Scheme 13A).[24a] To this end, a formal [3+2] cycloaddition of **64** and **65** proceeded at room temperature in the presence of catalytic **66** under irradiation with blue LED light to provide 2,5-dihydrooxazoles **67**. Subsequent DDQ-mediated oxidation provided the corresponding triaryloxazoles **51** with three different aryl groups in a one-pot operation, which could be utilized for the synthesis of cyclooxygenase-2 inhibitor **51a.** Furthermore, in 2016, Cho and coworkers synthesized triaryloxazoles **51b** and **51c** from α-bromoketone **58a** and benzylamine derivatives **49** by means of a Ru-photoredox catalyst under blue LED light irradiation (Scheme 13B).[24b]

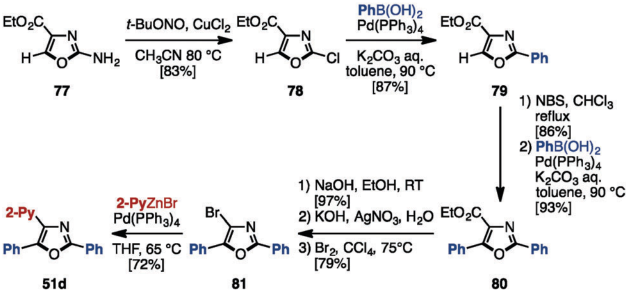
To construct an isoxazole core, 1,3-dipolar cycloaddition of aryl nitrile oxides with alkenes or alkynes has been used.[25] In 2013, Shetty and coworkers reported the synthesis of 3,4,5-triarylisoxazoles **70** by a 1,3-dipolar cyclization of nitrile oxide (prepared *in situ* from oxime **68**) and styrene to give isoxazole **69**, followed by bromination and Suzuki–Miyaura cross-coupling (Scheme 14A).[26a] In 2005, the group of Denmark synthesized triarylisoxazoles **70** by performing a 1,3-dipolar cyclization of phenylethynyl silyl ether **71** with **72** to give **73**, followed by Hiyama cross-coupling with aryl iodides (Scheme 14B).[26b] Elaborating this further, in 2011, Vasam, Vadde and coworkers achieved an NHC-catalyzed regioselective 1,3-dipolar cycloaddition of diarylacetylenes **74** and aryl nitrile *N*-oxides **75** to afford triarylisoxazoles **70** regioselectively (Scheme 14C).[26c]

Cross-coupling

As mentioned above, the cross-coupling reaction is a powerful method to construct aryl–aryl frameworks. However, examples



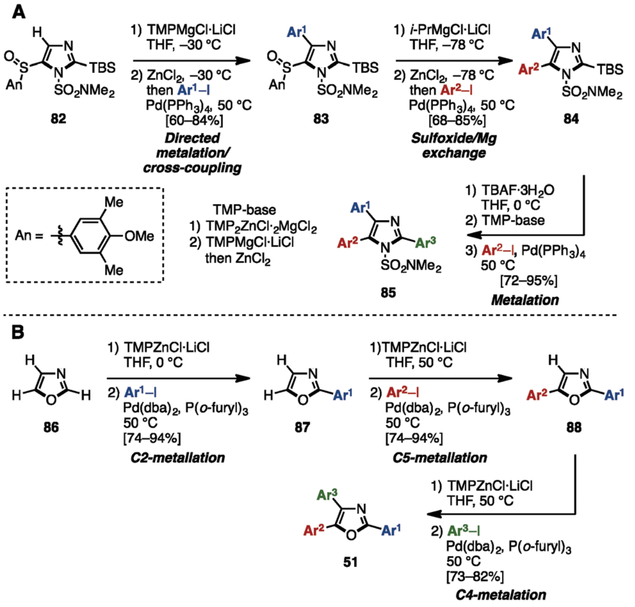
Scheme 14 1,3-Dipolar cycloaddition of nitrile oxides with alkenes or alkynes.



Scheme 15 Sequential cross-coupling of ethyl 2-chlorooxazole-4-carboxylate.

of multi-substituted azoles synthesized by cross-coupling reactions are quite rare,[27] due to the difficulty in accessing metalated azoles and halogenated azoles (they are less stable compared to those of pyrroles and thiophenes). One of few examples was reported in 2002, when Hodgetts and coworkers synthesized triaryloxazoles from 2-chlorooxazole-4-carboxylate (**78**) by using a sequence of regiocontrolled halogenation and Pd-catalyzed Suzuki–Miyaura coupling (Scheme 15).[27b] Intermediate **78** was prepared from 2-aminooxazole **77** by treatment with *t*-BuONO and $CuCl_2$. **78** was then coupled with phenylboronic acid under Pd catalysis, giving 2-phenyloxazole **79**. Treatment of **79** with *N*-bromosuccinimide (NBS) provided a C5-brominated oxazole, which was subjected to a second cross-coupling with phenylboronic acid to afford 2,5-diphenyloxazole **80**. After hydrolysis of the ester in **80**, the resulting carboxylic acid was converted to bromooxazole **81** *via* a Hunsdiecker reaction. Lastly, Negishi coupling of **81** with 2-pyridylzinc bromide gave triaryloxazole **51d**.

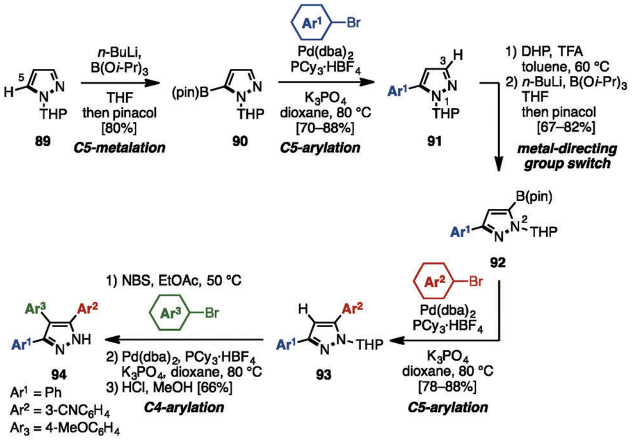
In 2013, Knochel and coworkers achieved an exhaustive functionalization of imidazole scaffolds by a combination of chemoselective direct metalation and sulfoxide/magnesium exchange (Scheme 16A).[28] Imidazole **82** was designed as the key intermediate of this transformation, in which the *N*,*N*-dimethylsulfamoyl group worked as an *ortho*-directing group and the 4-methoxy-3,5-dimethylbenzenesulfinyl (AnS(O)) group enabled direct metalation to the C4-position. After direct metalation, AnS(O) can be replaced by sulfoxide/magnesium exchange. This synthesis began with the selective metalation of **82** at the C4-position by using TMPMgCl·LiCl, followed by transmetalation of Mg with Zn, and Negishi coupling with aryl iodides to give 4-arylimidazoles **83**. Treatment of **83** with i-PrMgCl·LiCl promoted a sulfoxide/magnesium exchange, giving the corresponding Mg species. As with the C4-functionalization, a sequence of transmetalation of the resulting Mg species to Zn and then Negishi coupling yielded 4,5-diarylimidazoles **84**. Finally, after removal of the TBS group of **84**, deprotonation by TMPMgCl·LiCl (which required transmetalation with $ZnCl_2$ before cross-coupling) or by $TMP_2ZnCl\cdot 2MgCl_2\cdot 2LiCl$ at the C2 position, followed by Negishi coupling, furnished sulfonated triarylimidazoles **85** with three different aryl groups.



Scheme 16 (A) Selective metalation and sulfoxide/magnesium exchange. (B) Regioselective sequential metalation of oxazoles.

In the same year, the same group applied a sequence of regioselective metalations and cross-coupling reactions for the synthesis of triaryloxazoles **51** from simple oxazole (**86**) (Scheme 16B).[29] The use of TMPZnCl·LiCl as a metalation reagent and appropriately controlling the reaction temperature enabled regioselective metalations at the C1-, C4-, and C3-positions of oxazoles to give the corresponding zincated oxazoles. These intermediates were then reacted with aryl iodides in the presence of catalytic $Pd(dba)_2/P(o\text{-furyl})_3$ to provide arylated oxazoles. As a result, triaryloxazoles **51** could be synthesized regioselectively from simple oxazole (**86**) in three metalation/cross-coupling sequences.

In 2008, McLaughlin and coworkers developed a synthesis of 3,4,5-triarylpyrazoles using a switchable metal-directing group [a tetrahydropyran (THP) group], which enabled direct sequential lithiation of the C3- and C5-positions of the pyrazole core (Scheme 17).[30] First, THP-protected pyrazole **89** was lithiated

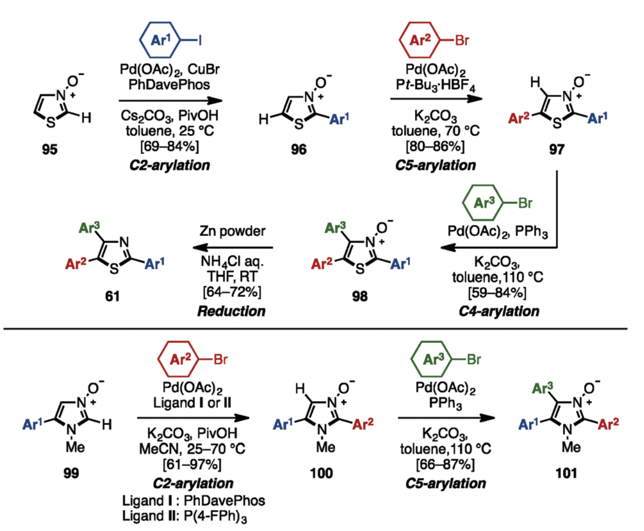


Scheme 17 Synthesis of 3,4,5-triarylpyrazole by using a switchable metal-directed group.

by n-BuLi at the C5-position, followed by treatment with B(Oi-Pr)$_3$ and pinacol, providing 5-borylpyrazole **90** regioselectively. Subsequent cross-coupling reaction with aryl bromides proceeded to furnish 5-arylpyrazoles **91**. By moving the metal-directing group (THP) from N1 to N2, the site of lithiation on the pyrazole core was shifted from C5 to C3. Taking advantage of this selectivity, a sequence of lithiation and borylation afforded 5-boryl-3-arylpyrazole **92**, which was coupled with aryl bromides to give 3,5-diarylpyrazoles **93**. Lastly, 3,4,5-triarylpyrazole **94** was synthesized by treatment of **93** with a sequence of bromination, cross-coupling, and removal of the THP group.

C–H arylation

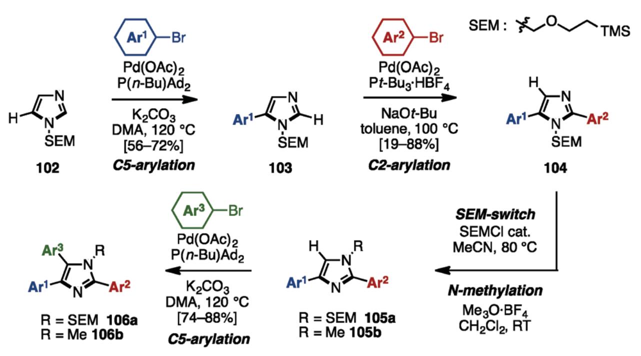
To avoid pre-functionalization and the use of unstable metallo-1,3- and 1,2-azoles, C–H arylation of azoles is one recent solution for the synthesis of multi-arylated azoles. In 2009, Fagnou and coworkers developed regioselective multiple C–H arylations of azole *N*-oxides (Scheme 18).[31] The *N*-oxide group not only enhanced the reactivity at all positions of azole derivatives, but also enabled a differentiated reactivity of C2 and C5 positions. First, C2-arylation of thiazole *N*-oxide (**95**) with aryl iodides proceeded at room temperature in the presence of catalytic Pd(OAc)$_2$, PhDavephos, CuBr, Cs$_2$CO$_3$, and PivOH in toluene to afford 2-arylthiazole *N*-oxides **96** with virtually complete regioselectivity. The addition of CuBr suppressed the production of a C5/C2 doubly arylated product. Since the C2 position was blocked, thiazole *N*-oxide **96** underwent a highly selective C5-arylation using catalytic Pd(OAc)$_2$/P(t-Bu)$_3$ and K$_2$CO$_3$ in toluene to provide 2,5-diarylthiazole *N*-oxides **97**. C4-arylation of **97** with aryl bromides proceeded in the presence of Pd(OAc)$_2$, PPh$_3$, and K$_2$CO$_3$ in toluene, giving triarylthiazole *N*-oxide **98**. Finally, thiazole *N*-oxide **98** could be deoxygenated to triarylthiazole **61** by treatment with Zn powder and aqueous NH$_4$Cl in THF. This protocol is applicable to the synthesis of triarylimidazole *N*-oxides **101** as well.



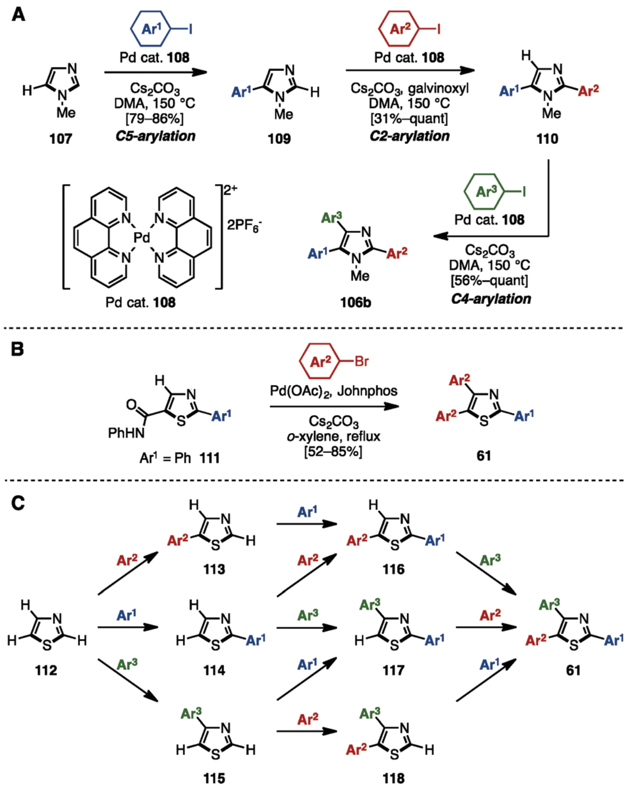
Scheme 18 Regioselective sequential C–H arylation of azole *N*-oxides.

In 2010, Sames and coworkers reported a regioselective sequential C–H arylation of SEM-protected imidazole **102** by using a ''SEM-switch'' strategy (Scheme 19).[32] This strategy transfers a SEM group from the N-1 to the N-3 nitrogen atom and thus enables a switch of the reaction site on imidazole cores. First, C5-arylation of **102** with aryl bromide proceeded in the presence of Pd(OAc)$_2$, P(n-Bu)Ad$_2$, and K$_2$CO$_3$ in dimethylacetamide (DMA) to provide 5-arylimidazoles **103**. Subsequently, **103** was coupled with aryl bromides under Pd(OAc)$_2$/P(t-Bu)$_3$ catalysis using NaOt-Bu as a base to furnish 2,5-diarylimidazoles **104** with complete regioselectivity. By means of a SEM-switch or *N*-alkylation, the reactive site of **104** was shifted to the C5 position of **105a** or **105b** (previously the C4 position of **102**). Finally, C5-arylation of **105a** and **105b** proceeded under the same reaction conditions as the first arylation step, giving triarylimidazoles **106a** and **106b**.

In 2011, Murai/Shibahara and coworkers reported a multiple regiocontrolled C–H arylation of simple 1,3-azoles such as *N*-methylimidazole (**107**), oxazole, and thiazole by [Pd(phen)$_2$](PF$_6$)$_2$ catalyst **108** (Scheme 20A).[33] For example, **107** was coupled with aryl iodides in the presence of **108** as a catalyst to afford 5-arylimidazoles **109**. Treatment of **109** with aryl iodides and catalyst **108** yielded 2,5-diarylimidazoles **110** with high regioselectivity when galvinoxyl was used as an additive. A subsequent reaction also using Pd catalyst **108** enabled the C4-arylation of **110**, providing



Scheme 19 Regioselective sequential C–H arylation of SEM-protected imidazoles.



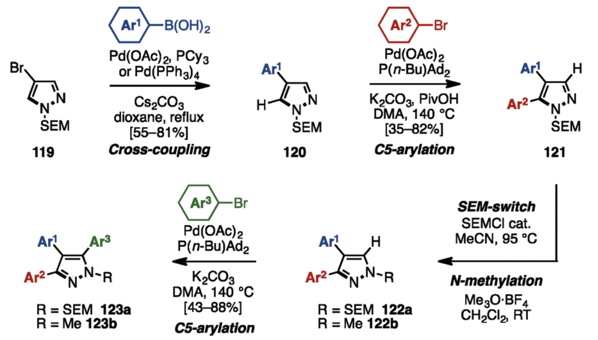
Scheme 20 (A) Multiple regioselective direct arylation of simple azoles, (B) C–H arylation of 5-thiazolecarboxanilide and (C) programmed synthesis of arylthiazoles.

triarylimidazoles **106b**. This three-step sequence was applicable not only to the sequential regioselective triarylation of thiazole, but also to the synthesis of Tie-2 tyrosine kinase inhibitor **11** (see Fig. 1).

In 2003, Miura and coworkers reported the diarylation of 2-phenyl-5-thiazolecarboxyanilide (**111**) at the C4 and C5 positions with concomitant decarbamoylation (Scheme 20B).[34] The reaction of **111** with aryl bromides in the presence of $Pd(OAc)_2$, Johnphos, and Cs_2CO_3 in refluxing *o*-xylene afforded the diarylated product, triarylthiazoles **61**, with two different aryl groups by decarbamoylation and C–H arylations of thiazoles.

In 2014, Itami and coworkers achieved a programmed synthesis of arylthiazoles *via* sequential direct C–H arylation reactions (Scheme 20C).[35] Although the synthesis of triarylthiazoles from 2-phenylthiazole by C–H arylation was already a known method at the time,[36] all possible substitution patterns of arylthiazoles **113–118** and **61** could be synthesized using this synthetic protocol from simple thiazole (**112**) *via* 11 distinct routes. Furthermore, this method enabled not only a gram-scale synthesis of triarylthiazole **61** with three different aryl groups, but also the preparation of over 150 different arylthiazoles.

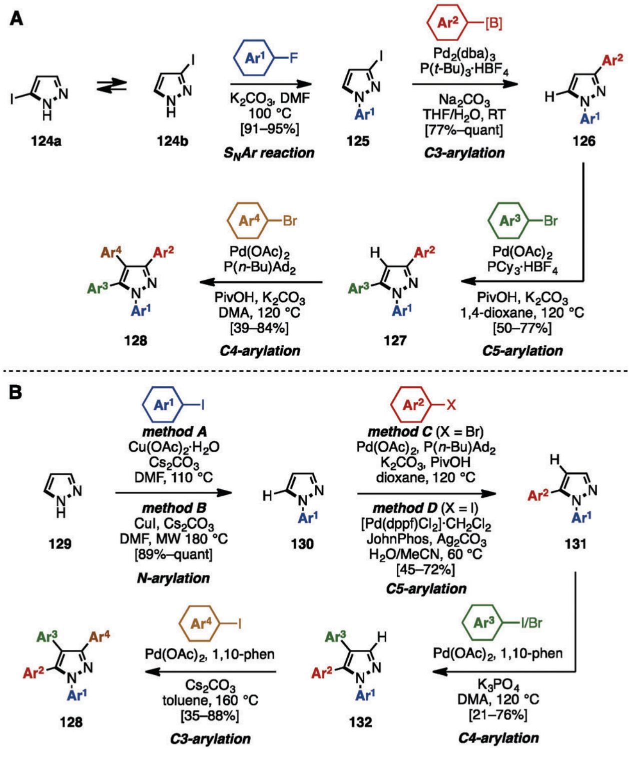
The SEM-switch strategy (see Scheme 19) developed by Sames and coworkers was also applicable to the synthesis of triarylpyrazoles **120** (Scheme 21).[37] The synthesis began with a cross-coupling reaction of 4-bromopyrazole **119** with arylboronic acids, giving 4-arylpyrazoles **120**. Treatment of **120** with aryl bromides in the presence of $Pd(OAc)_2$, $P(n\text{-}Bu)Ad_2$, K_2CO_3, and



Scheme 21 Regioselective sequential C–H arylation of SEM-protected pyrazoles.

PivOH in *N*,*N*-dimethylacetamide (DMA) provided 4,5-diarylpyrazoles **121**. A SEM-switch or *N*-methylation of **121** afforded 3,4-diarylpyrazoles **122a** or **122b**, which were coupled with aryl bromides to furnish triarylpyrazoles **123a** or **123b** with three different aryl substituents.

In 2015, Fuse and coworkers reported the regioselective synthesis of 1,3,4,5-tetraarylpyrazoles using a sequence of S_NAr, cross-coupling, and C–H arylation reactions, in which 3-iodo-1*H*-pyrazole **124** was selected as a starting material (Scheme 22A).[38] Iodopyrazole **124** was a mixture of tautomers **124a** and **124b**, however, S_NAr reaction of **124** with aryl fluorides provided *N*-arylpyrazole **125** as a single isomer. Subsequent cross-coupling of **125** with arylboronic acids or arylpinacol esters using catalytic



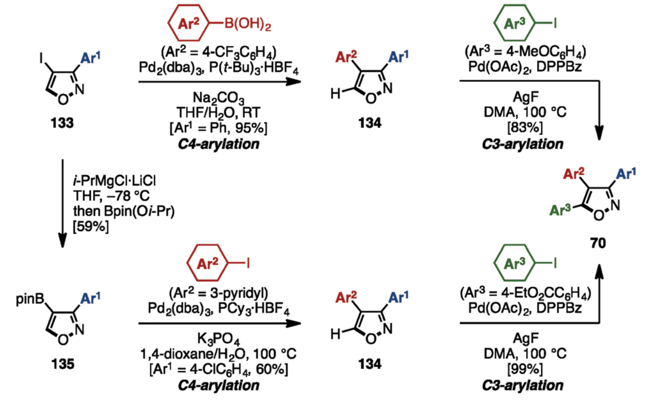
Scheme 22 (A) Sequential S_NAr/C–H arylation/cross-coupling of iodopyrazoles and (B) four-fold regioselective direct arylation for the synthesis of tetraarylpyrazoles.

$Pd_2(dba)_3/P(t\text{-}Bu)_3$ furnished 3-arylpyrazoles **126**. C5-arylation of **126** with aryl bromides occurred in the presence of $Pd(OAc)_2$, PCy_3, K_2CO_3, and PivOH in 1,4-dioxane to afford 1,3,5-triarylpyrazole **127**. By changing the ligand and solvent from PCy_3 and 1,4-dioxane to $P(n\text{-}Bu)Ad_2$ and DMA, C4-arylation of **127** proceeded to afford tetraarylpyrazole **128** with virtually complete isomeric purities.

In 2016, the same group achieved the synthesis of 1,3,4,5-tetraarylpyrazole **128** by using four-fold regioselective direct arylation reactions of simple pyrazole (**129**), including N–H arylation and three C–H arylations (Scheme 22B).[39] First, pyrazole (**129**) was subjected to Cu-catalyzed N–H arylation, providing *N*-arylpyrazoles **130** in excellent yields using a choice of two conditions (method A or B). A regioselective C5-arylation of **130** was then accomplished by selecting the reaction conditions (method C or D) depending on the substituent (Ar^2) of the aryl halide component to furnish 1,5-diarylpyrazoles **131** in moderate to good yields. C4-arylation of **131** with aryl iodides or aryl bromides proceeded in the presence of $Pd(OAc)_2$, 1,10-phenanthroline (1,10-phen), and K_3PO_4 in DMA to afford 1,4,5-triarylpyrazole **132**. Finally, the synthesis of 1,3,4,5-tetraarylpyrazoles **128** was achieved by treatment with aryl iodides in a $Pd(OAc)_2$/1,10-phen catalytic system.

In the same year, Fuse/Nakamura and coworkers accomplished the synthesis of triarylisoxazoles **70** by a sequence of cross-coupling and C–H arylation reactions (Scheme 23).[40] This synthesis began with a cross-coupling reaction of 4-iodo-3-phenylisoxazole **133** with an arylboronic acid, giving 3,4-diarylisoxazole **134** in excellent yield.

Subsequent C–H arylation at the C5-position of isoxazole using a procedure developed by Sasai and Takenaka[41] furnished triarylisoxazole **70** with three different aryl groups. In an alternative reaction sequence, 4-iodoisoxazole **133** was reacted with "turbo Grignard" reagent (i-PrMgCl·LiCl) in THF at −78 °C to produce a 4-isoxazolyl anionic species, which was readily trapped by Bpin(Oi-Pr) to give boronate **135**. A sequential cross-coupling of **135** with two different aryl iodides afforded triarylisoxazole **70** as well.



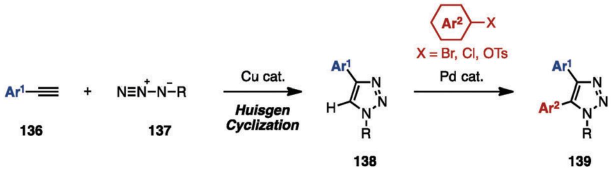
Scheme 23 Synthesis of triarylisoxazoles by cross-coupling and C–H arylation reactions.

Fully arylated polyazoles

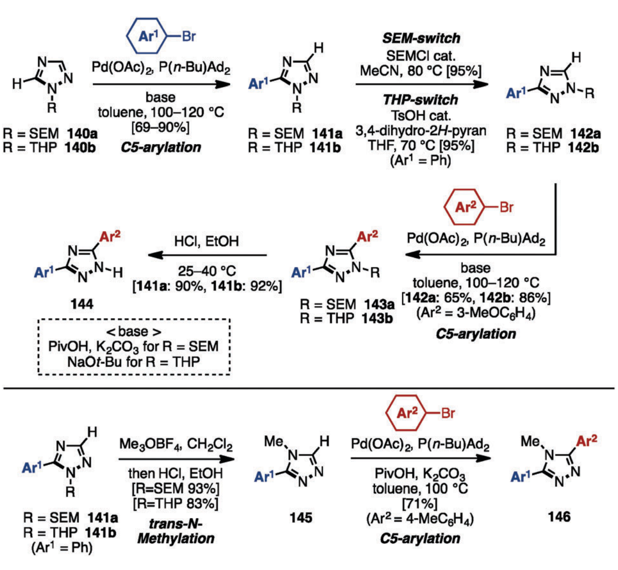
C–H arylation

Substituted 1,2,3-triazoles are conventionally constructed by using the Huisgen cyclization of alkynes and azides under Cu catalysis.[42] The synthesis of multiply arylated 1,2,3-triazoles can be achieved using the same method (Scheme 24). For example, arylacetylenes **136** were reacted with organic azides **137** in the presence of a Cu catalyst to provide 4-aryl-1,2,3-triazole **138**, which was then subjected to C–H arylation with arylating agents, giving 4,5-diaryl-1,2,3-triazoles **139**. As a pioneering work in the field of C–H arylation of 1,2,3-triazoles, Gevorgyan and coworkers reported a direct Pd-catalyzed arylation of 1,2,3-triazoles with aryl bromides.[42a] In Pd-catalyzed C–H arylations of 1,2,3-triazoles, aryl chlorides can be used as an arylating reagent under microwave irradiation, which was disclosed by Yorimitsu/Oshima and coworkers.[42b] Furthermore, Ackermann and coworkers developed Pd-catalyzed C–H arylations of 1,2,3-triazoles with aryl chlorides[42c] and aryl tosylates.[42d]

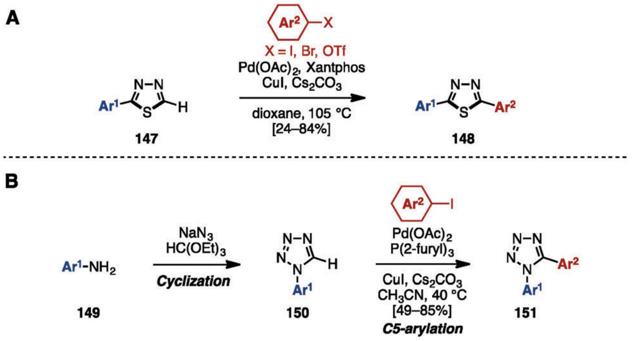
While realizing a SEM-switch strategy (see Schemes 19 and 21), the Sames group also achieved the synthesis of regioisomers of diaryl-1,2,4-triazoles such as (NH)-free diaryltriazole **144** and 4-alkylated diaryltriazole **146** (Scheme 25).[43] First, C5-arylation of 1-alkyl-1,2,4-triazoles **140** was accomplished. Treatment of **140** with aryl bromides in the presence of catalytic $Pd(OAc)_2$ and $P(n\text{-}Bu)Ad_2$ using a combination of PivOH and K_2CO_3



Scheme 24 Synthesis of 4,5-diaryl-1,2,3-triazoles by Huisgen cyclization/C–H arylation.



Scheme 25 C–H arylation of 1,2,4-triazole by SEM and a THP switch strategy.



Scheme 26 (A) C–H arylation of thiadiazoles by C–H arylation and (B) cycloaddition and C–H arylation for the synthesis of diaryltetrazoles.

(for **140a**) or NaO*t*-Bu (for **140b**) provided 5-aryl-1,2,4-triazoles **141a** and **141b** in high yields. To switch the reactivity for C–H arylation to the C3 position of the 1,2,4-triazole scaffold, SEM or THP groups were transferred from the N1 to the N2 position, upon which a second arylation provided 3,5-diaryl-1,2,4-triazoles **143**. The removal of SEM or THP groups under acidic conditions furnished (NH)-free diaryltriazole **144**.

In addition, when 1-alkyl-5-aryltriazoles **141** were reacted with Meerwein's reagent (Me_3OBF_4), *trans-N*-methylation occurred on the N4 nitrogen atom, giving 4-methyl-4*H*-triazole **145** as a single regioisomer. Finally, 4-alkylated diaryltriazole **146** was synthesized by one last arylation.

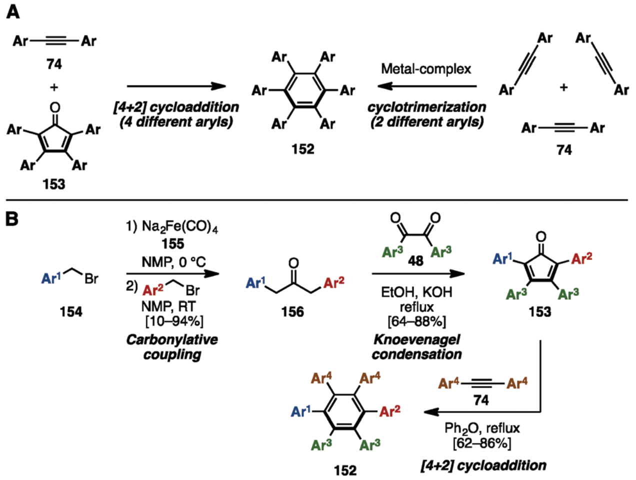
In 2012, Eycken and coworkers reported a Pd/Cu-catalyzed C–H arylation of 1,3,4-thiadiazoles with aryl iodides, bromides, and triflates (Scheme 26A).[44] For example, 2-aryl-1,3,4-thiadiazoles **147** was treated with aryl halides in the presence of $Pd(OAc)_2$, Xantphos, CuI, and Cs_2CO_3 as a base in dioxane to provide 2,5-diaryl-1,3,4-thiadiazoles **148**.

In 2010, Pour and coworkers reported a Pd-catalyzed C–H arylation of 1-aryltetrazoles **150** for the synthesis of 1,5-diaryltetrazoles **151** (Scheme 26B).[45] By using a cyclization reaction of aniline derivatives **149**, sodium azide, and triethyl orthoformate, 1-aryltetrazole **150** was easily prepared. The subsequent C5-arylation of **150** with aryl iodides proceeded in the presence of $Pd(OAc)_2$, $P(2\text{-furyl})_3$, CuI, and Cs_2CO_3 to provide 1,5-diaryltetrazoles **151**. In this catalytic system, the presence of the phosphine ligand is essential to stabilize the intermediate Pd^{II} species.

Hexaarylbenzenes (HABs)

Cyclization

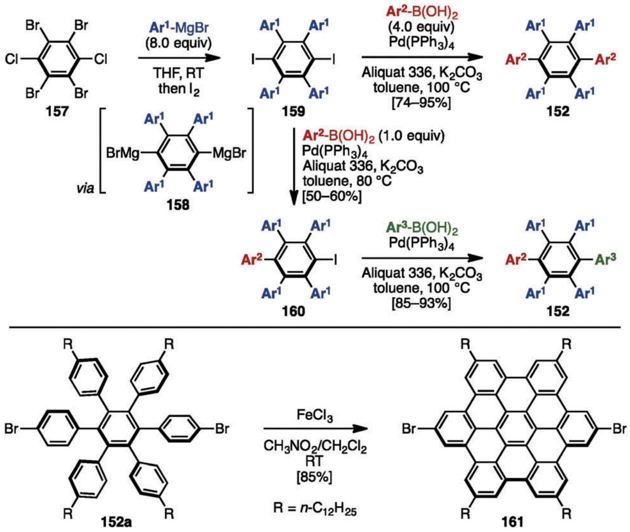
Hexaarylbenzene (HAB), a fully arylated form of benzene, is a propeller-shaped, radially π-extended molecule. HABs show exceptional structural diversity when different aryl groups are appended, resulting in a wide range of applications in materials science.[46] To synthesize HABs **152** with the same or a few different aryl groups, there are two well-known reactions, involving (1) a [4+2] cycloaddition reaction of tetraarylcyclopentadienones **153** and diarylacetylenes **74** or (2) a metal-catalyzed [2+2+2] cyclotrimerization of **74** (Scheme 27A). For example, in 2007, Hughes and a coworker established a synthetic protocol for unsymmetrical HAB **152** with a maximum of four different aryl groups by preparing unsymmetrical **153** (Scheme 27B).[47] The carbonylative coupling of two different benzyl bromide derivatives **154** using $Na_2Fe(CO)_4$ (Collman's reagent: **155**) as a carbonylative reagent provided unsymmetrical diarylacetones **156**. This was then converted to tetraarylcyclopentadienones **153** with three different aryl groups *via* Knoevenagel condensation with symmetrical diaryldiketones **48**. The Diels–Alder reaction of **153** with symmetrical diarylacetylenes **74** furnished HABs **152** bearing four different aryl substituents. The key to making such highly substituted HABs is the unsymmetrical carbonylative coupling step: since unsymmetrical ketones **156** can only be obtained if the reaction of the first benzyl bromide with Collman's reagent is complete before addition of the second benzyl bromide, careful examination of the reaction rates were necessary.



Scheme 27 (A) Conventional methods for the synthesis of HABs and (B) a representative protocol for unsymmetrical HABs.

Cross-coupling and C–H arylation

In 2008, Mullen and coworkers reported the synthesis of symmetrically and unsymmetrically substituted HABs **152** by using Hart's benzyne-mediated arylation protocol[48] and Suzuki–Miyaura cross-coupling reactions (Scheme 28).[49] Treatment of 1,2,4,5-tetrabromo-3,6-dichlorobenzene (**157**) with excess arylmagnesium bromide led to the formation of a dimagnesium intermediate **158**, which was directly quenched with iodine to provide tetraarylated diiodobenzenes **159**.[49] Subsequent cross-coupling with excess arylboronic acid (4.0 equiv.) using Aliquat 336 as a phase-transfer catalyst in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in toluene at 100 °C provided symmetrically substituted HABs **152** in high yields. In contrast, treatment of **159** with only 1.0 equivalent of arylboronic acid at 80 °C furnished mono-coupled product **160**, which was then coupled with another arylboronic acid to afford unsymmetrical HABs **152** bearing four different aryl groups. As HABs are promising precursors for the synthesis of hexabenzocoronenes (HBC), which are privileged structures in materials science, dehydrogenative cyclization of

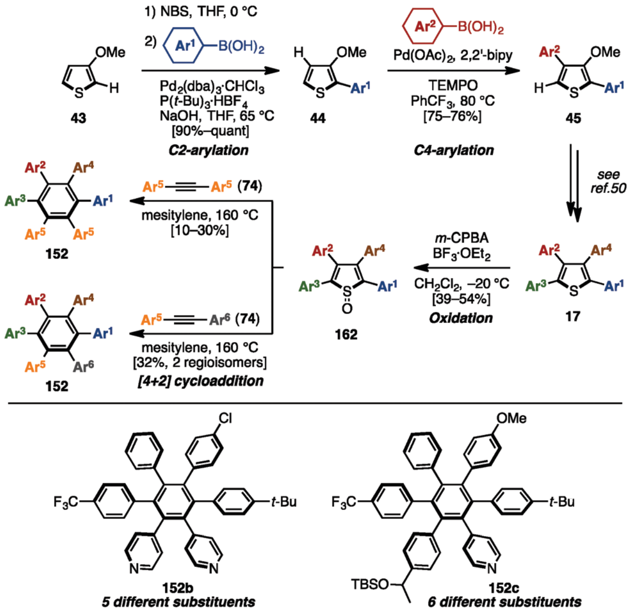


Scheme 28 Synthesis of symmetrical and unsymmetrical HABs by using Hart's benzyne-mediated arylation protocol and Suzuki–Miyaura cross-coupling.

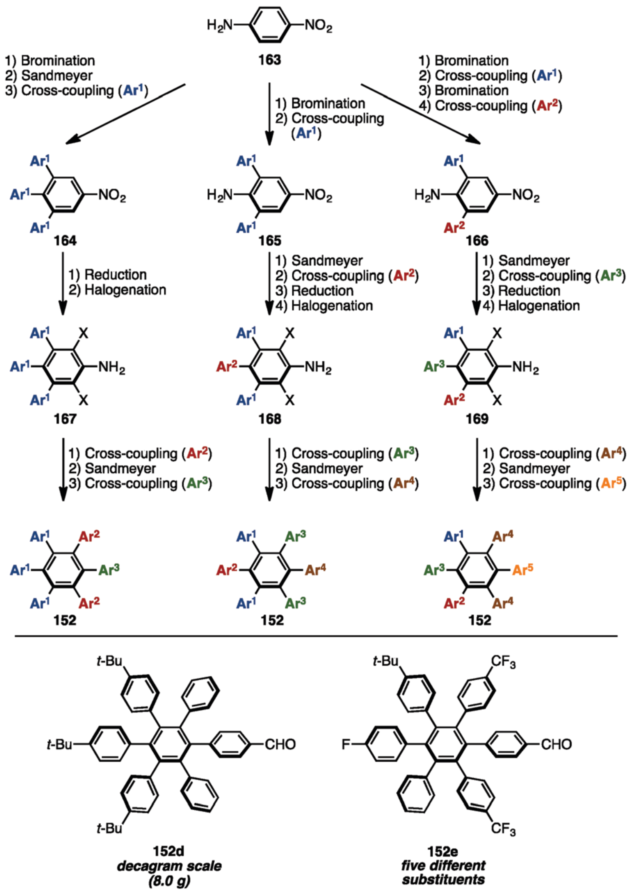
HAB **152a** was demonstrated by using $FeCl_3$, producing the corresponding HBC **161**.

In 2015, Yamaguchi, Itami and coworkers achieved the synthesis of HABs with five or six different substituents using C–H arylation, cross-coupling and [4+2] cycloaddition (Scheme 29).[50] Initially, their previous synthesis of tetraarylthiophenes **17** with four different aryl groups (see Scheme 9) was modified to allow for a scalable synthesis. First, the Rh-catalyzed C–H arylation of 3-methoxythiophene (**43**) was changed to a bromination/Suzuki–Miyaura cross-coupling to eliminate the use of an expensive Rh-catalyst. Next, the Pd-catalyzed C–H arylation of **44** with iodoarenes was changed to a Pd-catalyzed C–H arylation of **44** with arylboronic acids in order to achieve better β-selectivity at lower temperatures. After these modifications, a gram-scale synthesis of tetraarylthiophenes **17** was achieved. Then, treatment of **17** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in the presence of $BF_3{\cdot}OEt_2$ oxidized the thiophene to the corresponding thiophene *S*-oxide **162** to enhance the reactivity of the thiophene moiety as a diene. Subsequent [4+2] cycloaddition of **162** with symmetrical diarylacetylenes **74** at 160 °C provided HABs **152b** with five different aryl groups. When unsymmetrical diarylacetylene **74** was employed, HABs **152c** with six different aryl substituents were synthesized as a mixture of regioisomers. Regioisomers can be separated by chromatography, and the structure of **152c** was assigned by X-ray crystal structure analysis. This was the first example of a synthesis of HAB with five or six different aryl groups in a programmable manner.

In 2016, Jux and coworkers presented a multi-gram synthesis of uncommon HABs starting from *p*-nitroaniline (**163**) by utilizing a combination of electrophilic halogenation, Sandmeyer bromination, and Suzuki–Miyaura cross-coupling reactions, calling it a "functionalization of *para*-nitroaniline" (FpNA) (Scheme 30).[51] This synthetic protocol enabled the preparation of 26 different substitution patterns of HABs, of which 18 geometries including five different aryl groups were inaccessible by means of well-established methods. Moreover, this strategy was applicable to the large-scale synthesis of HABs (*e.g.*, **152d** was synthesized on an 8.0 g scale).



Scheme 29 Synthesis of HABs through [4+2] cycloaddition of tetraarylthiophene *S*-oxides with diarylacetylenes.



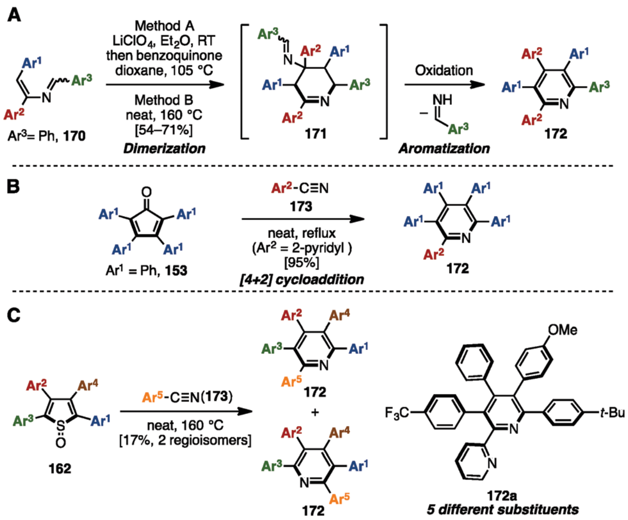
Scheme 30 Synthesis of uncommon HABs by a "FpNA protocol".

Fully arylated pyridines and pyrimidines

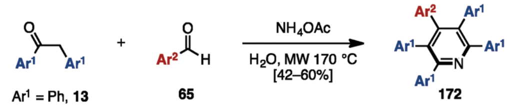
Cyclization

Adding to its utility in benzene synthesis, the [4+2] cycloaddition reaction is a powerful tool to construct pyridines. In 2001, Palacios and coworkers reported the dimerization of 2-azadienes **170** in the presence of lithium perchlorate or under thermal conditions for the synthesis of pentaarylpyridines **172** (Scheme 31A).[52a] In this reaction, 2-azadienes **170** worked as both a dienophile and a diene to dimerize into tetrahydropyridines **171** *via* [4+2] cycloaddition, which was readily converted to the corresponding pyridines **172** or dihydropyridines accompanied by an elimination of imines and/or oxidation. Under lithium perchlorate conditions, dihydropyridines could be obtained (depending on the substituents on the pyridine core), which were immediately oxidized with benzoquinone to give pentaarylpyridines **172**. Additionally, in 2008, Draper and coworkers synthesized pentaarylpyridine **172** using a [4+2] cycloaddition reaction of tetraarylcyclopentadienone **153** (tetracyclone: Ar^1 = Ph) with arylnitrile (Ar^2 = 2-pyridyl) **173** as a dienophile (Scheme 31B).[52b] To this end, treatment of **153** with 2-arylnitrile **173** under reflux conditions provided pentaarylpyridine **172** with two different aryl groups in excellent yield. Furthermore, in 2015, Yamaguchi and Itami demonstrated a pentaarylpyridine synthesis by [4+2] cyclization of thiophene *S*-oxides **162** (see Scheme 29) with arylnitriles **173** (Scheme 31C). Although the yields and regioselectivities for the [4+2] cycloaddition were low, this protocol allowed for the synthesis of pentaarylpyridines **172** such as **172a** with five different aryl groups.

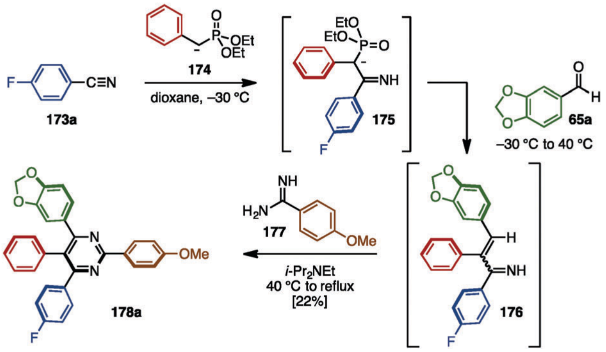
In 2009, Tu and coworkers reported a microwave-assisted multicomponent reaction for pentaarylpyridines **172** from 1,2-diphenylethanone (**13**) and benzaldehyde derivatives **65** (Scheme 32).[53] Treatment of **13** with several benzaldehyde derivatives **64** in the presence of NH_4OAc and H_2O under microwave irradiation at 170 °C furnished pentaarylpyridines **172** in moderate yields.



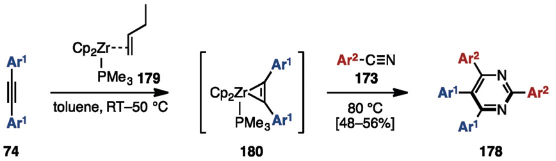
Scheme 31 Synthesis of pentaarylpyridines by [4+2] cyclization reactions.



Scheme 32 Microwave-assisted pyridine synthesis.



Scheme 33 Cyclization of *in situ*-generated α,β-unsaturated imine and amidine.



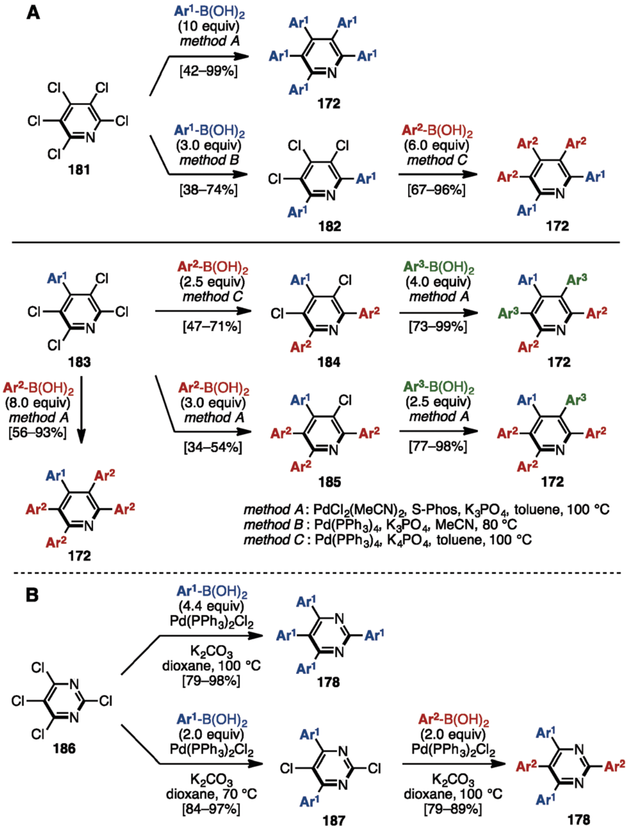
Scheme 34 Zirconium-mediated multicomponent reactions.

In the case of fully arylated pyrimidines, in 2005, Kiselyov reported a one-pot synthesis of polysubstituted pyrimidines including tetraarylated pyrimidine **178a** by cyclization of *in situ*-generated α,β-unsaturated imines and amidines (Scheme 33).[54] This one-pot sequence began with the nucleophilic addition of phosphorus ylide **174** to arylnitrile **173a** to yield ylide **175**. Subsequent Horner–Wadsworth–Emmons reaction with aldehyde **65a** furnished α,β-unsaturated imine **176**. Lastly, **176** was cyclized with amidine **177** in the presence of i-Pr_2NEt to provide tetraarylpyrimidine **178a** with four different aryl groups, albeit in low yield.

In 2013, Liu and coworkers reported zirconium-mediated multicomponent reactions of diarylacetylene **74** with arylnitriles **173**, which enabled a regioselective synthesis of tetraarylpyrimidines **178** (Scheme 33).[55] Diarylacetylenes **74** reacted with zirconocene **179** to form a phosphine-stabilized zirconocene–alkyne complex **180**, which was readily coupled with aryl nitriles **173**, giving tetraarylpyrimidines **178** in moderate yields (Scheme 34).

Cross-coupling

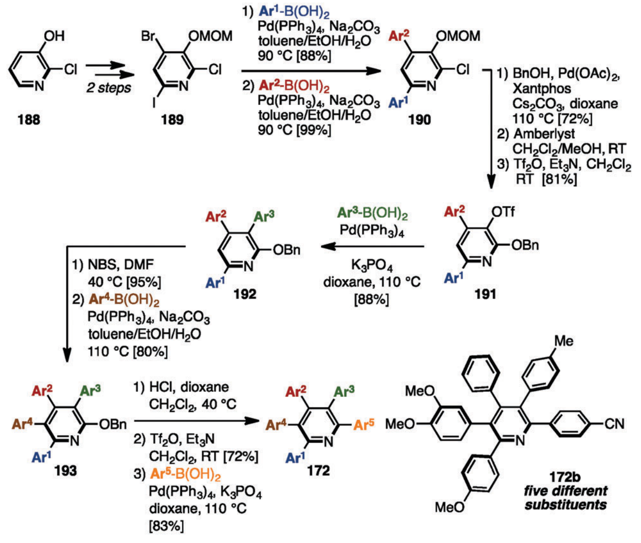
Similarly to the synthesis of tetraarylpyrroles and thiophenes (see Scheme 4), in 2014, Langer and coworkers synthesized a series of pentaarylpyridines by multiple Suzuki–Miyaura cross-coupling reactions of pentachloropyridine (**181**) (Scheme 35A).[56] Treatment of **181** with excess arylboronic acid in the presence of $PdCl_2(MeCN)_2$, S-Phos, and K_3PO_4 in toluene at 100 °C (method A) provided pentaarylpyridines **172** with one type of aryl group. When the reaction was performed with fewer equivalents of arylboronic acid under $Pd(PPh_3)_4$ and K_3PO_4 in MeCN at 80 °C



Scheme 35 (A) Synthesis of pentaarylpyridines by multiple Suzuki–Miyaura cross-couplings and (B) synthesis of tetraarylpyrimidines in a similar manner.

(method B), the cross-coupling reaction occurred at only the C2- and C6-positions of the pyridine scaffold. Then, by switching the solvent from MeCN to toluene, and increasing the reaction temperature (method C), pentaarylpyridines **172** with two different aryl substituents were successfully synthesized. Moreover, starting from 4-aryl-2,3,5,6-tetrachloropyridine **183**, this sequential cross-coupling protocol provided pentaarylpyridines **172** with two or three different aryl groups in one- or two-step operations. In addition, Langer and coworkers reported the synthesis of tetraarylpyrimidines **178** from tetrachloropyrimidine (**186**) in a similar manner (Scheme 35B).

In 2014, Schmitt and coworkers established a synthetic route toward multiply arylated pyridines bearing up to five different aryl groups, which involved five-fold sequential and regioselective Suzuki–Miyaura cross-coupling reactions starting from commercially available 2-chloro-3-hydroxypyridine (**188**) (Scheme 36).[57] 2,4,6-Trihalogenated pyridine **189**, which was readily prepared from **188** in two steps, was coupled with two different arylboronic acids to furnish 4,6-diarylpyridine **190** regioselectively. Then, installation of a benzyloxy group, removal of a MOM group, and triflation of the resulting hydroxy group afforded 2-(benzyloxy)-pyridine **191**. The third cross-coupling event converted **191** into 3,4,6-triarylpyridine **192**, which was then brominated and cross-coupled at the C5-position to provide 3,4,5,6-tetraarylpyridine **193**. Finally, after removal of the benzyl group, the resulting



Scheme 36 Synthesis of pentaarylpyridines with five different aryl groups by fully regiocontrolled Suzuki–Miyaura cross-coupling.

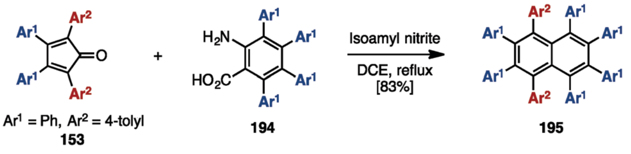
2-hydroxypyridine was triflated and coupled with an arylboronic acid to yield pentaarylpyridines **172** such as **172a** with five different substituents in a total of 13 steps.

Others

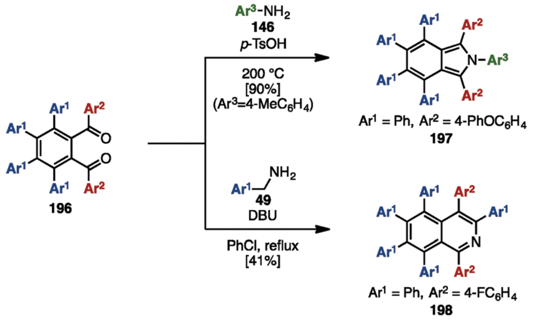
In 2000, Pascal and coworkers synthesized octaarylnaphthalene **195** with two different aryl substituents by [4+2] cycloaddition of tetraarylcyclopentadienone **153** and tetraarylbenzyne (Scheme 37).[58] The [4+2] cycloaddition of **153** (Ar^1 = Ph, Ar^2 = 4-tolyl) with tetraarylbenzyne, which was readily generated by treatment of tetraarylanthranilic acid **194** with isoamyl nitrile, provided octaarylnaphthalene **195** with two different aryl groups in 83% yield.

In the 1990s, syntheses of heptaarylisoindole **197**[59a] and heptaarylisoquinoline **198**[59b] were reported by Hay and coworkers *via* the condensation of 1,2-bis(benzoyl)benzene **196** with aniline derivatives **146** or benzylamine derivative **48**, respectively (Scheme 38). Treatment of **196** (Ar^1 = Ph, Ar^2 = 4-PhOC$_6$H$_4$) with excess **146** (Ar^3 = 4-MeC$_6$H$_4$) using *p*-toluenesulfonic acid (*p*-TsOH) at 200 °C furnished isoindole **197** in 90% yield. When benzylamine **49** was reacted with **196** and DBU in chlorobenzene under reflux conditions, heptaarylated isoquinoline **198** was also synthesized (41% yield).

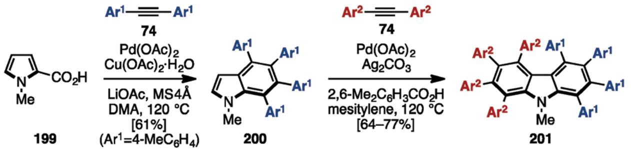
In 2009, Miura and coworkers reported Pd-catalyzed oxidative coupling reactions of *N*-substituted pyrroles and their carboxylic



Scheme 37 [4+2] cycloaddition of tetraarylcyclopentadienone and tetraarylbenzyne.



Scheme 38 Synthesis of hexaarylisoindole and heptaarylisoquinoline.



Scheme 39 Synthesis of multiply arylated carbazoles using Pd-catalyzed oxidative coupling reactions with diarylalkynes.

acid derivatives with diarylacetylenes (Scheme 39).[60] Treatment of **199** with diarylacetylene **74** in the presence of $Pd(OAc)_2$, $Cu(OAc)_2$, LiOAc, and MS4Å in dimethylacetamide (DMA) provided tetraarylated indole **200**. When using Ag_2CO_3 and 2,6-dimethylbenzoic acid as an oxidant and an additive instead of $Cu(OAc)_2 \cdot H_2O$ and LiOAc, the second coupling reaction of **200** with diarylacetylenes **74** proceeded to furnish octaarylcarbazoles **201** with two different aryl substituents.

Conclusions

This article summarized methodologies developed for the synthesis of fully arylated arenes with more than two different aryl substituents, including 5-membered (hetero)arenes, 6-membered (hetero)arenes, and fused polycyclic (hetero)arenes. Although the synthesis of structurally beautiful but complex fully arylated arenes has been facilitated over many decades, application of these molecules in materials and biological sciences is still rare. It is our hope that new methodologies to access unexploited molecules will continue to aid the discovery of new functional materials.

Acknowledgements

This work was supported by JSPS KAKENHI Grant No. JP16H01011, JP16H04148, JP16K13085, and 16H01140 (to J. Y.), and a JSPS research fellowship for young scientists (to S. S.). We thank Dr Yoshihiro Ishihara (Vertex Pharmaceuticals) for fruitful discussion and critical comments.

Notes and references

1 Selected examples, (*a*) E. L. Williams, K. Haavisto, J. Li and G. E. Jabbour, *Adv. Mater.*, 2007, **19**, 197; (*b*) F. Li, Z. Chen, W. Wei, H. Cao, Q. Gong, F. Teng, L. Qian and Y. Wang, *J. Phys. D: Appl. Phys.*, 2004, **37**, 1613; (*c*) B. S. Ong, Y. Wu, P. Liu and S. Gardner, *J. Am. Chem. Soc.*, 2004, **126**, 3378; (*d*) K. Shin-ya, K. Wierzba, K. Matsuo, T. Ohtani, Y. Yamada, K. Furihata, Y. Hayakawa and H. Sato, *J. Am. Chem. Soc.*, 2001, **123**, 1262.

2 R. Rossi, F. Bellina, M. Lessi, C. Manzini and L. Perego, *Synthesis*, 2014, 2833.

3 Selected examples, (*a*) K. R. J. Thomas, M. Velusamy, J. T. Lin, C. H. Chuen and Y. T. Tao, *J. Mater. Chem.*, 2005, **15**, 4453; (*b*) J. Kido, K. Hongawa, K. Okuyama and K. Nagai, *Appl. Phys. Lett.*, 1993, **63**, 2627; (*c*) K. SuzukiK. UenoA. Senoo*JP. Pat.*,109765 A,2003; (*d*) S. Miwatashi, Y. Arikawa, K. Naruo, K. Igaki, Y. Watanabe, H. Kimura, T. Kawamoto and S. Ohkawa, *Chem. Pharm. Bull.*, 2005, **53**, 410; (*e*) N. W. Johnson, M. Semones, J. L Adams, M. Hansbury and J. Winkler, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5514; (*f*) S. H. Lee, H. J. Seo, M. J. Kim, S. Y. Kang, S.-H. Lee, K. Ahn, M. Lee, H.-K. Han, J. Kim and J. Lee, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6632.

4 (*a*) L. Knorr, *Ber.*, 1884, **17**, 2863; (*b*) C. Paal, *Ber.*, 1884, **17**, 2756.

5 (*a*) W.-J. Kuo, Y.-H. Chen, R.-J. Jeng, L.-H. Chan, W.-P. Lin and Z.-M. Yang, *Tetrahedron*, 2007, **63**, 7086; (*b*) C.-S. Li, Y.-H. Tsai, W.-C. Lee and W.-J. Kuo, *J. Org. Chem.*, 2010, **75**, 4004; (*c*) S. Mao, X.-Q. Zhu, Y.-R. Gao, D.-D. Guo and Y.-Q. Wang, *Chem. – Eur. J.*, 2015, **21**, 11335; (*d*) S. Mao, Y.-R. Gao, S.-L. Zhang, D.-D. Guo and Y.-Q. Wang, *Eur. J. Org. Chem.*, 2015, 876.

6 I. Bergner and T. Opatz, *J. Org. Chem.*, 2007, **72**, 7083.

7 X. Wu, K. Li, S. Wang, C. Liu and A. Lei, *Org. Lett.*, 2016, **18**, 56.

8 (*a*) T. T. Dang, R. Ahmad, T. T. Dang, H. Reinke and P. Langer, *Tetrahedron Lett.*, 2008, **49**, 1698; (*b*) F. Yang, T. Jin, M. Bao and Y. Yamamoto, *Tetrahedron*, 2011, **67**, 10147; (*c*) Y. Dang and Y. Chen, *J. Org. Chem.*, 2007, **72**, 6901; (*d*) T. T. Dang, N. Rasool, T. T. Dang, H. Reinke and P. Langer, *Tetrahedron Lett.*, 2007, **48**, 845; (*e*) Đ. T. Tùng, Đ. T. Tuân, N. Rasool, A. Villinger, H. Reinke, C. Fischer and P. Langer, *Adv. Synth. Catal.*, 2009, **351**, 1595.

9 A. Rahimi, J. C. Namyslo, M. H. H. Drafz, J. Halm, E. Hübner, M. Nieger, N. Rautzenberg and A. Schmidt, *J. Org. Chem.*, 2011, **76**, 7316.

10 F. Yang, T. Jin, M. Bao and Y. Yamamoto, *Tetrahedron*, 2011, **67**, 10147.

11 (*a*) S. Ishikawa, Y. Noda, M. Wada and T. Nishikata, *J. Org. Chem.*, 2015, **80**, 7555; (*b*) T. Nishikata, Y. Yamane, Y. Yamaguchi and S. Ishikawa, *Asian J. Org. Chem.*, 2016, **5**, 466.

12 (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*b*) L.-C. Campeau, R. Stuart and K. Fagnou, *Aldrichimica Acta*, 2007, **40**, 35; (*c*) T. Satoh and M. Miura, *Chem. Lett.*, 2007, **36**, 200; (*d*) I.-V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*e*) I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036; (*f*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (*g*) F. Bellina and R. Rossi, *Tetrahedron*, 2009, **65**, 10269; (*h*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (*i*) O. Daugulis, *Top. Curr. Chem.*, 2010, **292**, 57; (*j*) J. Roger, A. L. Gottumukkala and H. Doucet, *ChemCatChem*, 2010, **2**, 20; (*k*) M. Livendahl and A. M. Echavarren, *Isr. J. Chem.*, 2010, **50**, 630; (*l*) Y.-X. Su and L.-P. Sun, *Mini-Rev. Org. Chem.*, 2012, **9**, 87; (*m*) L. Ackermann, A. R. Kapdi, H. K. Potuchi and S. I. Kozhushkov, *Handbook of Green Chemistry*, Wiley-VCH, Weinheim, 2012, vol. 7, p. 259; (*n*) A. Sharma, D. Vacchani and E. Van der Eycken, *Chem. – Eur. J.*, 2013, **19**, 1158; (*o*) R. Rossi, F. Bellina, M. Lessi and C. Manzini, *Adv. Synth. Catal.*, 2014, **356**, 17.

13 M. Nakano, H. Tsurugi, T. Satoh and M. Miura, *Org. Lett.*, 2008, **10**, 1851.

14 S. Yanagisawa, K. Ueda, H. Sekizawa and K. Itami, *J. Am. Chem. Soc.*, 2009, **131**, 14622.

15 (*a*) S. Yanagisawa, T. Sudo, R. Noyori and K. Itami, *J. Am. Chem. Soc.*, 2006, **128**, 11748; (*b*) K. Ueda, K. Amaike, R. M. Maceiczyk, K. Itami and J. Yamaguchi, *J. Am. Chem. Soc.*, 2014, **136**, 13226; (*c*) A. D. Yamaguchi, K. M. Chepiga, J. Yamaguchi, K. Itami and H. M. L. Davies, *J. Am. Chem. Soc.*, 2015, **137**, 644.

16 S. Yanagisawa and K. Itami, *Tetrahedron*, 2011, **67**, 4425.

17 (*a*) S. Samanta, D. Roy, S. Khamarui and D. K. Maiti, *Chem. Commun.*, 2014, **50**, 2477; (*b*) R. Sarkar and C. Mukhopadhyay, *Eur. J. Org. Chem.*, 2015, 1246; (*c*) R. Sarkar and C. Mukhopadhyay, *Tetrahedron Lett.*, 2015, **56**, 3872; (*d*) P. Hu, Q. Wang, Y. Yan, S. Zhang, B. Zhang and Z. Wang, *Org. Biomol. Chem.*, 2013, **11**, 4304.

18 (*a*) W. Pei, S. Li, X. Nie, Y. Li, J. Pei, B. Chen, J. Wu and X. Ye, *Synthesis*, 1998, 1298; (*b*) P. C. Patil, F. A. Luzzio and D. R. Demuth, *Tetrahedron Lett.*, 2015, **56**, 3039.

19 C. Kison and T. Opatz, *Chem. – Eur. J.*, 2008, **15**, 843.

20 (*a*) H. Bredereck, R. Gompper and D. Hayer, *Chem. Ber.*, 1953, **86**, 88; (*b*) H. Bredereck and R. Bangert, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 662.

21 (*a*) J. L. Bailey and R. R. Sudini, *Tetrahedron Lett.*, 2014, **55**, 3674; (*b*) J. S. Carter, D. J. Rogier, M. J. Graneto, K. Seibert, C. M. Koboldt, Y. Zhang and J. J. Talley, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1167.

22 Y.-L. Tsai, Y.-S. Fan, C.-J. Lee, C.-H. Huang, U. Das and W. Lin, *Chem. Commun.*, 2013, **49**, 10266.

23 J. Xuan, L.-Q. Lu, J. R. Chen and W.-J. Xiao, *Eur. J. Org. Chem.*, 2013, 6755.

24 (*a*) T.-T. Zeng, J. Xuan, W. Ding, K. Wang, L.-Q. Lu and W.-J. Xiao, *Org. Lett.*, 2015, **17**, 4070; (*b*) T. Chatterjee, J. Y. Cho and E. J. Cho, *J. Org. Chem.*, 2016, **81**, 6995.

25 F. Hu and M. Szostak, *Adv. Synth. Catal.*, 2015, **357**, 2583.

26 (*a*) R. Shetty, S. Shafi and Y. Kuberan, *J. Pharma Res.*, 2013, **6**, 897; (*b*) S. E. Denmark and J. M. Kallemeyn, *J. Org. Chem.*, 2005, **70**, 2839; (*c*) S. Kankala, R. Vadde and C. S. Vasam, *Org. Biomol. Chem.*, 2011, **9**, 7869.

27 (*a*) B. Clapham and A. J. Sutherland, *J. Org. Chem.*, 2001, **66**, 9033; (*b*) K. J. Hodgetts and M. T. Kershaw, *Org. Lett.*, 2002, **4**, 2905; (*c*) I. C. Christoforou and P. A. Koutentis, *Org. Biomol. Chem.*, 2007, **5**, 1381.

28 C. Sämann, E. Coya and P. Knochel, *Angew. Chem., Int. Ed.*, 2013, **53**, 1430.

29 D. Haas, M. Mosrin and P. Knochel, *Org. Lett.*, 2013, **15**, 6162.

30 M. McLaughlin, K. Marcantonio, C.-Y. Chen and I. W. Davies, *J. Org. Chem.*, 2008, **73**, 4309.

31 (*a*) L.-C. Campeau, M. Bertrand-Laperle, J.-P. Leclerc, E. Villemure, S. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 3276; (*b*) L.-C. Campeau, D. R. Stuart, J.-P. Leclerc, M. Bertrand-Laperle, E. Villemure, H.-Y. Sun, S. Lasserre, N. Guimond, M. Lecavallier and K. Fagnou, *J. Am. Chem. Soc.*, 2009, **131**, 3291.

32 J. M. Joo, B. B. Touré and D. Sames, *J. Org. Chem.*, 2010, **75**, 4911.

33 (*a*) F. Shibahara, E. Yamaguchi and T. Murai, *J. Org. Chem.*, 2011, **76**, 2680; (*b*) F. Shibahara, T. Yamauchi, E. Yamaguchi and T. Murai, *J. Org. Chem.*, 2012, **77**, 8815.

34 A. Yokooji, T. Okazawa, T. Satoh, M. Miura and M. Nomura, *Tetrahedron*, 2003, **59**, 5685.

35 S. Tani, T. N. Uehara, J. Yamaguchi and K. Itami, *Chem. Sci.*, 2014, **5**, 123.

36 (*a*) G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2007, **46**, 7996; (*b*) S. K. Kim, J.-H. Kim, Y. C. Park, J. W. Kim and E. K. Yum, *Tetrahedron*, 2013, **69**, 10990.

37 R. Goikhman, T. L. Jacques and D. Sames, *J. Am. Chem. Soc.*, 2009, **131**, 3042.

38 T. Morita, D. Kobayashi, K. Matsumura, K. Johmoto, H. Uekusa, S. Fuse and T. Takahashi, *Chem. – Asian J.*, 2015, **10**, 1626.

39 S. Fuse, T. Morita, K. Johmoto, H. Uekusa and H. Tanaka, *Chem. – Eur. J.*, 2015, **21**, 14370.

40 T. Morita, S. Fuse and H. Nakamura, *Angew. Chem., Int. Ed.*, 2016, **55**, 13580.

41 M. Shigenobu, K. Takenaka and H. Sasai, *Angew. Chem., Int. Ed.*, 2015, **54**, 9572.

42 (*a*) S. Chuprakov, N. Chernyak, A. S. Dudnik and V. Gevorgyan, *Org. Lett.*, 2007, **9**, 2333; (*b*) M. Iwasaki, H. Yorimitsu and K. Oshima, *Chem. – Asian J.*, 2007, **2**, 1430; (*c*) L. Ackermann, R. Vicente and R. Born, *Adv. Synth. Catal.*, 2008, **350**, 741; (*d*) L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2008, **48**, 201.

43 J. M. Joo, P. Guo and D. Sames, *J. Org. Chem.*, 2013, **78**, 738.

44 D. D. Vachhani, A. Sharma and E. Van der Eycken, *J. Org. Chem.*, 2012, **77**, 8768.

45 M. Špulák, R. Lubojacký, P. Šenel, J. Kuneš and M. Pour, *J. Org. Chem.*, 2010, **75**, 241.

46 V. Vij, V. Bhalla and M. Kumar, *Chem. Rev.*, 2016, **116**, 9565.

47 R. G. Potter and T. S. Hughes, *Org. Lett.*, 2007, **9**, 1187.

48 (*a*) H. Hart and P. Rajakumar, *Tetrahedron*, 1995, **51**, 1313; (*b*) K. Harada, H. Hart and C.-J. F. Du, *J. Org. Chem.*, 1985, **50**, 5524; (*c*) P. Rajakumar and A. Kannan, *Tetrahedron Lett.*, 1993, **34**, 8317.

49 X. Yang, X. Dou and K. Müllen, *Chem. – Asian J.*, 2008, **3**, 759.

50 S. Suzuki, Y. Segawa, K. Itami and J. Yamaguchi, *Nat. Chem.*, 2015, **7**, 227.

51 D. Lungerich, D. Reger, H. Hölzel, R. Riedel, M. M. J. C. Martin, F. Hampel and N. Jux, *Angew. Chem., Int. Ed.*, 2016, **55**, 5602.

52 (*a*) F. Palacios, C. Alonso, G. Rubiales and J. M. Ezpeleta, *Eur. J. Org. Chem.*, 2001, 2115; (*b*) C. M. A. Ollagnier, S. D. Perera, C. M. Fitchett and S. M. Draper, *Dalton Trans.*, 2008, 283.

53 B. Jiang, W.-J. Hao, X. Wang, F. Shi and S.-J. Tu, *J. Comb. Chem.*, 2009, **11**, 846.

54 A. S. Kiselyov, *Tetrahedron Lett.*, 2005, **46**, 1663.

55 X. You, S. Yu and Y. Liu, *Organometallics*, 2013, **32**, 5273.

56 S. Reimann, P. Ehlers, A. Petrosyan, S. Kohse, A. Spannenberg, A. E. Surkus, T. V. Ghochikyan, A. S. Saghyan, S. Lochbrunner, O. Kühn, R. Ludwig and P. Langer, *Adv. Synth. Catal.*, 2014, **356**, 1987.

57 C. Doebelin, P. Wagner, F. Bihel, N. Humbert, C. A. Kenfack, Y. Mely, J.-J. Bourguignon and M. Schmitt, *J. Org. Chem.*, 2014, **79**, 908.

58 R. A. Pascal Jr., L. Barnett, A. X. Qiao and D. M. Ho, *J. Org. Chem.*, 2000, **65**, 7711.

59 (*a*) Y. Ding and A. S. Hay, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 3293; (*b*) R. Singh and A. S. Hay, *Macromolecules*, 1992, **25**, 1033.

60 M. Yamashita, H. Horiguchi, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 7481.