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Review

Masuda Borylation–Suzuki Coupling (MBSC) Sequence: A One-Pot Process to Access Complex (hetero)Biaryls

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Abstract: The direct formation of (hetero)biaryls from readily available (hetero)aryl halides under mild reaction conditions can be efficiently achieved through the Masuda borylation–Suzuki coupling (MBSC) sequence. The MBSC sequence catenates Pd-catalyzed Masuda borylation and Suzuki coupling into a one-pot process, giving access to diverse symmetrically and unsymmetrically substituted scaffolds. (Hetero)biaryls are ubiquitous structural motifs that appear in natural products, pharmaceutically relevant scaffolds, functional dyes, and several other structures. This review summarizes the development of the MBSC sequence and its improvements over the past two decades.

Keywords: sequential palladium catalysis; one-pot reactions; Masuda borylation; Suzuki coupling; (hetero)aryl halides; (hetero)biaryls; multicomponent reactions

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1. Introduction

The formation of carbon–carbon bonds via metal-catalyzed cross-coupling reactions is of extraordinary interest and plays a key role in the construction of complex and functional (hetero)cyclic scaffolds, in industry as well as on a scientific laboratory scale [1]. In particular, the synthesis of (hetero)biaryls are the focus of current research, as the biaryl motif is ubiquitous in active ingredients, functional materials, and fine chemicals [2,3]. Thereby, to access biaryls, challenges in regio- and stereoselectivity [4] and increasing demands regarding resource-benign innovative, green syntheses [5–7] and complex substitution patterns [8,9] are recently described issues.

The development of novel cross-coupling methodologies has considerably affected current syntheses of pharmaceutically relevant natural products and analogues [10], agrochemicals [11], or functional dyes [12], as required for finding, investigation, and modulation of new or improved properties. Among transition metal-catalyzed cross-coupling reactions, the venerable Suzuki coupling is probably the most prominent and versatile method. The palladium-catalyzed Suzuki coupling is the reaction of an organoboron compound with a (hetero)aryl halide to form bi(hetero)aryls (Figure 1). The catalytic cycle starts with the oxidative addition of the (hetero)aryl halide to the palladium(0) complex (I), which is often the rate-determining step. After a cis–trans isomerization (II), a metathetic exchange takes place with suitable bases (III). This leads to a more electrophilic Pd-species. The organoboron compound forms an ate-complex with the base, enabling the now nucleophilic boron compound to transfer the organic moiety to the palladium complex in a transmetalation step (IV). Thereafter, a trans–cis isomerization (V) takes place and the cross-coupled compound is reductively eliminated (VI), and the palladium catalyst can react in a following catalytic cycle [13,14]. Due to its great impact in chemistry and neighboring natural sciences, Prof. Akira Suzuki, together with professors Richard F. Heck and Ei-ichi Negishi, was awarded the Nobel Prize in Chemistry in 2010 [1,15–17].

The desired organoboron compounds can be accessed in several ways, e.g., halogen–metal exchange of aryl bromides or iodides with organolithium or -magnesium species [18–20],

C-H activation with rhenium, rhodium, ruthenium or iridium catalysts [21], or the transition metal-catalyzed borylation of aryl halides [22]. In 1995, Miyaura published the first palladium-catalyzed borylation of aryl halides using bis(pinacolato)diboron [23]. The Miyaura borylation was consequently developed by Masuda via the exchange of bis(pinacolato)diboron with the more reactive and atom-economically more benign pinacolyl borane (Figure 2) [24]. To date, there are several tentative mechanistic rationales, although the mechanism of the Masuda borylation remains to be elucidated [25–27]. Masuda proposed that pinacoly borane oxidatively adds to the palladium complex (A I) before a transmetalation involving a σ-bond metathesis via a four-center transition state between the aryl halide and the palladium-boron species occurs (A II). In the course of this metathesis, the aryl boronic acid (ester) is formed. The palladium-catalyst is reduced in a base-mediated reductive elimination (A III) [25]. Lin published a rationale based on DFT calculations. After an oxidative addition of the aryl halide to the palladium complex (B I), an amine-assisted ionization leads to an electron-deficient Pd-species (B II). The aryl boron compound is formed in a σ-bond metathesis (B III) and the catalyst is recovered in a base-mediated reductive elimination (B IV) [26].

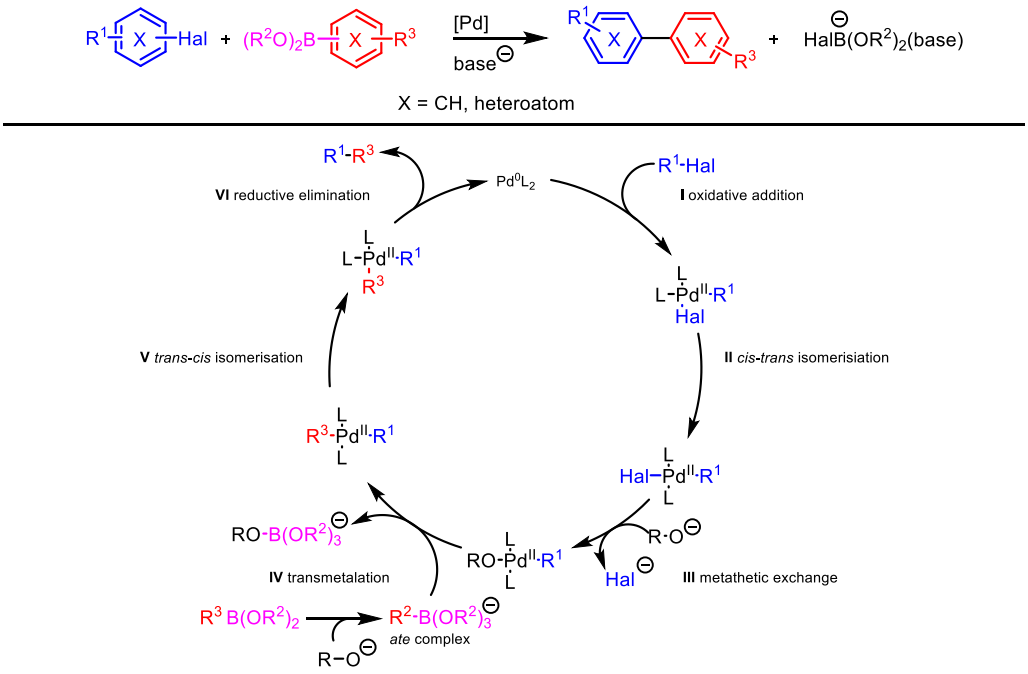


Figure 1. General scheme and mechanism of a Suzuki coupling.

Organic synthesis is steadily challenged with respect to efficiency and selectivity, both for ecological and economic reasons. One approach to address the theoretical concept of an "ideal synthesis" is the development of one-pot processes where several reaction steps are conducted in the same vessel without the isolation of intermediates, therefore reducing solvents and waste, also due to less purification operation and, thus, saving time and resources [28,29]. Due to the similarities between Suzuki coupling and Masuda borylation with respect to reaction conditions, such as palladium catalyst systems and employed solvents and bases, linking both reactions into a one-pot sequence was obvious (Figure 3). As a consequence, the Masuda borylation–Suzuki coupling (MBSC) sequence formally represents a catalytic cross-coupling of two (hetero)aryl halides employing pinacolyl borane as the formal reductant.

This review surveys the development of the Masuda borylation–Suzuki coupling (MBSC) sequence in the past twenty years, from its first development by Baudoin in the early 2000s [30] and constant improvements in different labs until our group exploited its full potential and turned the MBSC sequence into a versatile and reliable synthetic tool for

the construction of complex bi(hetero)aromatic scaffolds [31]. For the literature research, Google Scholar, Reaxys, Scifinder, and Web of Science have been used.

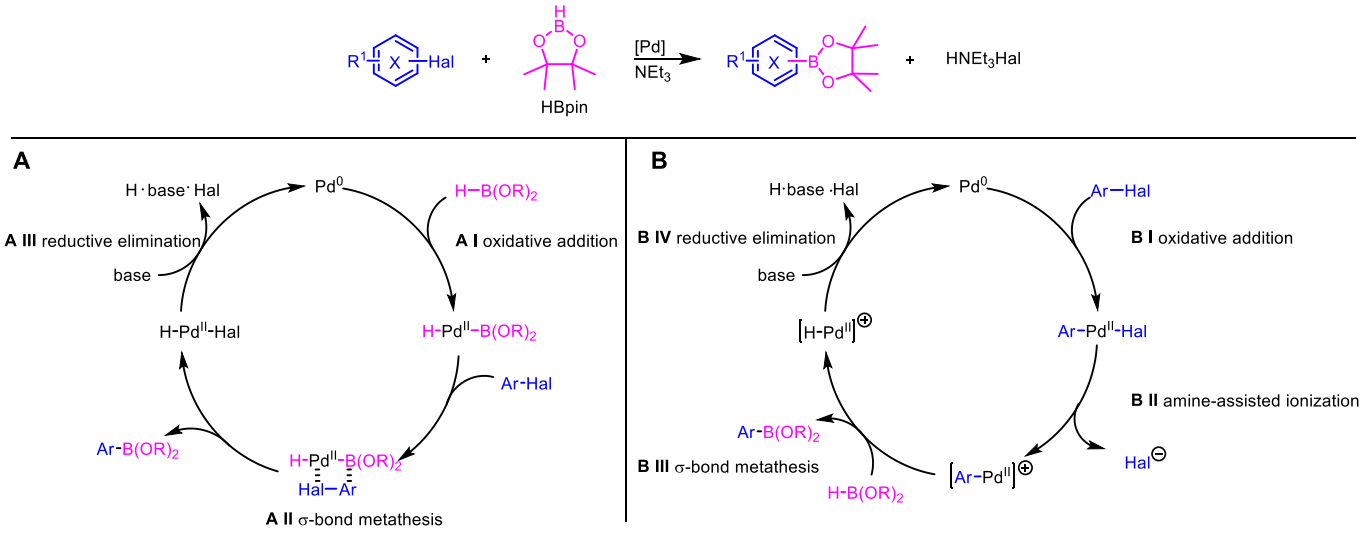


Figure 2. General scheme and proposed mechanisms by Masuda (**A**) and Lin (**B**) of a Masuda borylation.

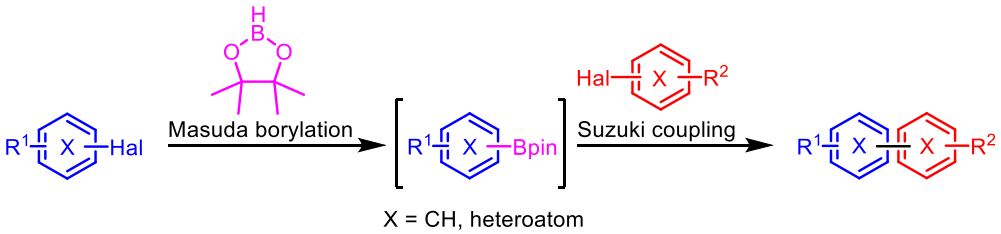


Figure 3. Linkage of Masuda borylation and Suzuki coupling into a one-pot MBSC sequence.

2. Synthesis

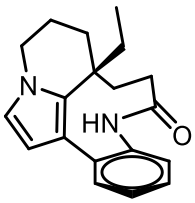
For the concatenation of Masuda borylation and Suzuki coupling into a MBSC sequence as an efficient and fast way to synthesize biaryl systems, a prerequisite is to identify suitable conditions ranging from the common catalyst system over solvent systems and employed bases to reaction conditions. Therefore, in the course of its development and continuous improvement, the MBSC protocol has been modified with respect to reaction conditions, ligands, and tolerated substrates or functional groups. The regioselectivity and influence of directing substituent effects have also been considered. As stated in the introduction, the overall value of the MBSC sequence is the opportunity to hold a powerful late-stage tool with broad functional group tolerance for the synthesis of functional bi(hetero)aryls in hand.

2.1. Baudoin's First One-Pot MBSC Synthesis of ortho,ortho'-Biaryls

Baudoin and coworkers were particularly interested in pharmaceutically active *ortho*-disubstituted biaryls. Their concept of the synthesis of the antimitotic natural product (-)-rhazinilam (**1**), isolated from various *apocynaceae* (Figure 4) and biphenyl analogues, consists of a Suzuki key step to form the *ortho*-disubstituted biaryl core.

They envisioned a reaction sequence involving a borylation reaction and a subsequent C-C-bond-forming step that allows the rapid construction of a library of analogues for biological screenings. The Masuda borylation of sterically hindered *ortho*-substituted phenyl bromides under standard conditions initially led to low yields, but after a catalyst screening and optimization studies on the addition of sterically hindered phosphane ligands, satisfactory yields could be achieved [32,33]. This encouraged Baudoin et al. to couple both Masuda borylation and Suzuki coupling into a one-pot process. 2-Bromoaniline

(**2a**) was transformed into the corresponding pinacolyl boronic acid ester with pinacolyl borane (HBpin) (**3**) in the presence of palladium (II) acetate and the sterically hindered ligand 2-(dicyclohexylphosphino)biphenyl (JohnPhos) (Figure 5) in a ratio of 4:1. Triethylamine as the base gave the best results. After 1 h at 80 °C, without the addition of fresh catalyst, water was added to scavenge the excess of the remaining **3**. The addition of 2-iodophenylacetonitriles **4** and the stronger base barium hydroxide led to the formation of biaryls **5a** (73%) and **5b** (66%) (Figure 5) [30].



(-)-rhazinilam (**1**)

Figure 4. Antimitotic alkaloid (-)-rhazinilam (**1**).

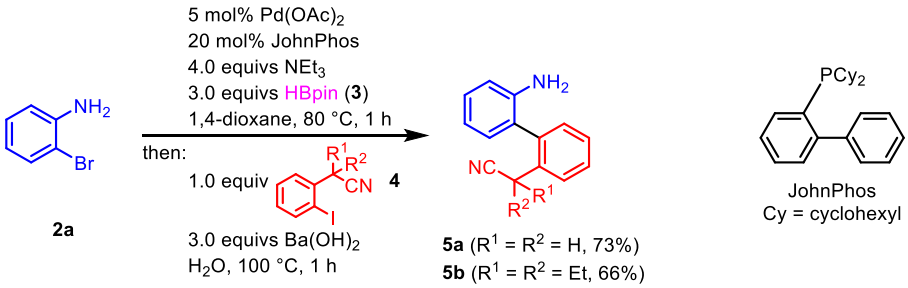


Figure 5. First concatenation of Masuda borylation and Suzuki coupling into a one-pot MBSC sequence by Baudoin et al. [30].

With these results in hand, several differently substituted derivatives **5** have been synthesized in yields ranging from 20 to 78% (Figure 6). After the deprotection of the methoxymethyl (MOM) protecting group, oxidation and lactamization was performed on Baudoin's route to rhazinilam analogues **5** [34].

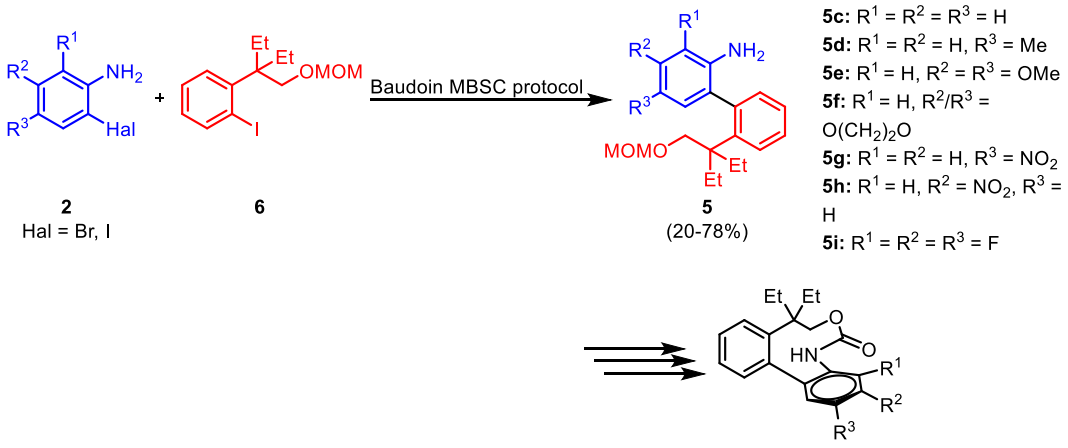


Figure 6. Synthesis of analogues of rhazinilam **5** via Baudoin's one-pot MBSC protocol [34].

In the study of synthetic routes to seven- or eight-membered biphenyl and 2-phenylindole lactams as potential kinase inhibitors, Baudoin et al. were able to employ heterocyclic halide substrates in the MBSC sequence for the first time using their standard protocol (Figure 7) [35].

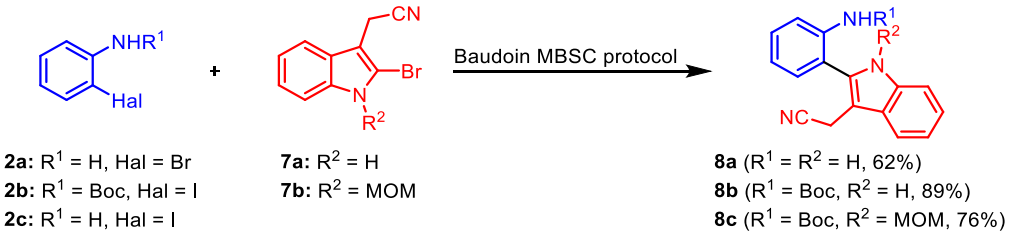


Figure 7. First employment of heterocycles in the one-pot MBSC sequence [35].

Additionally, Baudoin could establish a general consideration for the order of the borylation and the cross-coupling compound. It was found that the Masuda borylation step gives higher conversions with electron-rich substrates bearing electron-donating groups (EDG). It is expected that electron-rich aryl halides and electron-deficient organoboron compounds favor the σ-bond metathesis [26]. The resulting electron-rich boronate intermediates are more reactive in the transmetalation step of the Suzuki coupling. Fortunately, Suzuki coupling works best with electron-poor aryl halides with electron-withdrawing groups (EWG) (Figure 8).

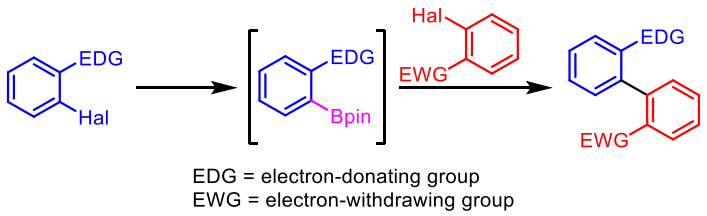


Figure 8. Order of the electronics of borylation and cross-coupling components in Baudoin's one-pot MBSC sequence [35].

2.2. Queiroz's One-Pot MBSC Sequence with Benzothiophene Substrates

Shortly after Baudoins' studies, Queiroz and coworkers became interested in the synthesis of thienocarbazoles as biologically active compounds or as biomarkers due to their fluorescence properties and their possible ability to intercalate into the DNA. The group used Baudoin's reaction conditions and extended the MBSC sequence to the synthesis of 2-methyl-2′-nitro biaryls **11**. Bromo-substituted benzothiophenes **9** were reacted in a Masuda borylation and subsequently in a Suzuki coupling with differently substituted *ortho*-nitrophenyl derivatives **10,** which gave the biaryls **11** in yields ranging from 50 to 80% (Figure 9). Queiroz's observations concerning the influence of electron-donating and electron-withdrawing substituents matched with Baudoins' results. Finally, the biaryls were reductively cyclized in a Cadogan cyclization with triethyl phosphite into the desired thienocarbazoles [36].

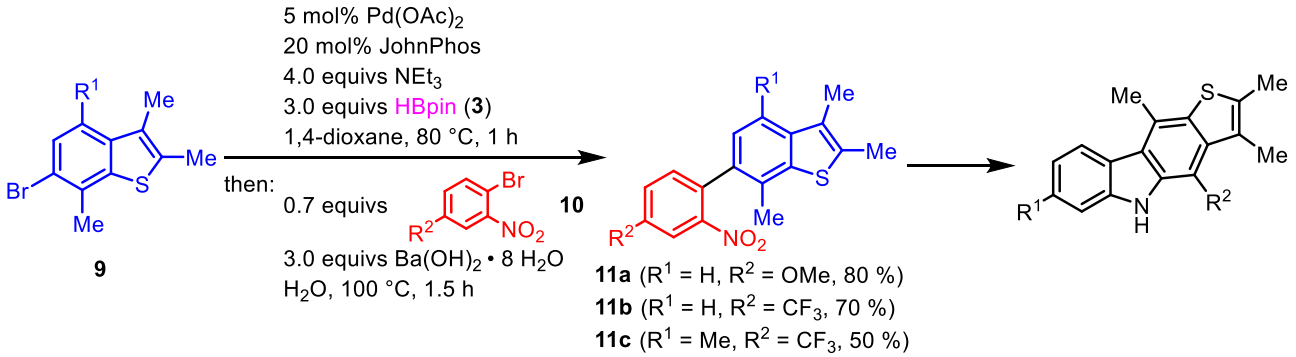


Figure 9. Queiroz' one-pot MBSC synthesis of 2-methyl-2′-nitro biaryls **11** [36].

Later, the synthesis of benzo[*b*]thienyldehydroamino acid esters **14** was approached. Starting from *ortho*-methyl- or *ortho*-methoxy-substituted bromobenzo[*b*]thiophenes **12,** after borylation, the subsequent Suzuki step was performed using β-bromo dehydroamino acid esters **13**. Thereby, Queiroz succeeded in extending the MBSC sequence to non-aromatic substrates. The regiochemistry of the starting material was strictly maintained. The group synthesized nine *E*- and *Z*-configurated benzo[*b*]thienyldehydroamino acids with yields ranging from 30 to 61% (Figure 10). The compounds were tested for their antimicrobial and fluorescence properties and showed activity against Gram-positive bacteria *B. cereus* and *B subtilis*. The luminescent derivatives might also be used as fluorescent probes [36,37].

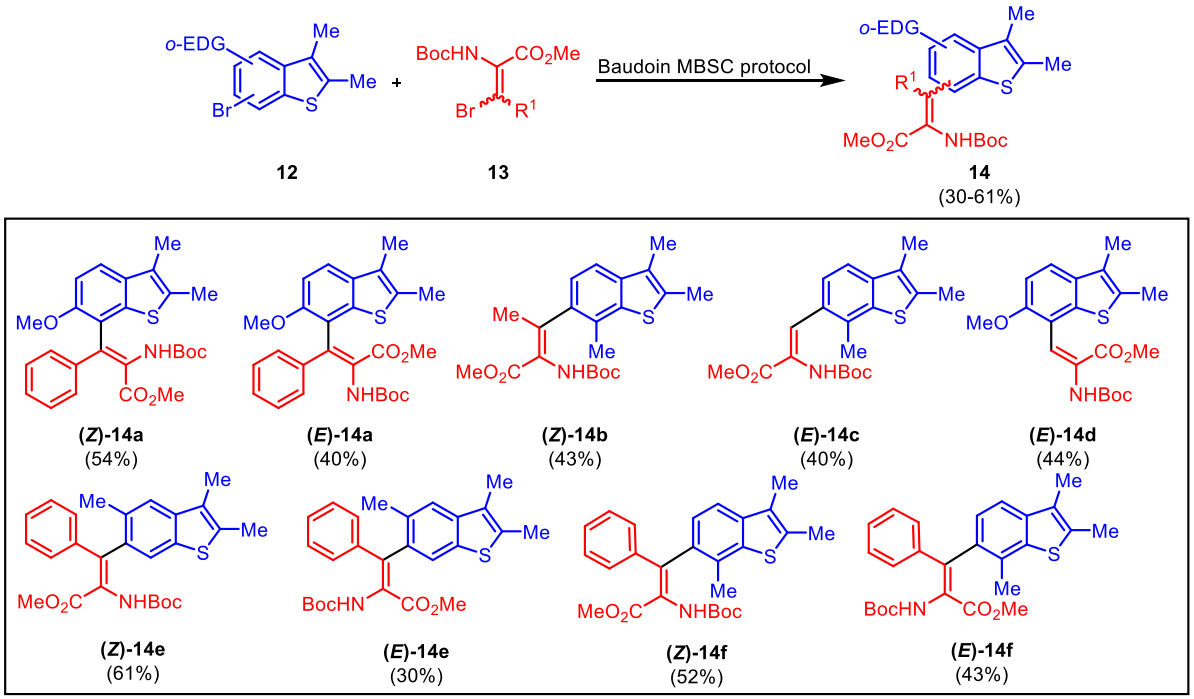


Figure 10. Queiroz' one-pot MBSC synthesis of benzo[*b*]thienyldehydroamino acid esters **14** [37,38].

Queiroz and coworkers could also establish a novel MBSC sequence with a concluding lactamization of the non-isolable Suzuki product of *ortho*-anilines **2** with bromothiophenes **12,** which gave the benzothieno [2,3-*c*]quinolin-6(5*H*)-ones **15**. The yields of these tetracyclic compounds range between 40 and 50% (Figure 11). The products have been investigated in DNA and polynucleotide binding studies [39].

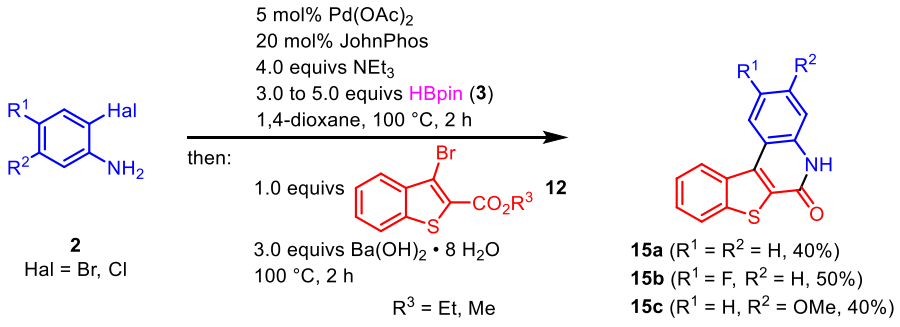


Figure 11. Queiroz' one-pot MBSC synthesis of benzothieno[2,3-*c*]quinolin-6(5*H*)-ones **15** [39].

2.3. Levacher's One-Pot MBSC Sequence with Naphthyl Substrates

In their studies on the development of novel axially chiral ligands, Levacher et al. were likewise interested in the lactamization of (hetero)biaryls and contributed to the advance-

ment of the MBSC sequence. The group was able to drastically simplify the borylation step in the sequence. After an optimization study, it was found that tetrakis(triphenylphosphine) palladium(0) led to significantly higher yields. Advantageously, no addition of bulky ligands was necessary. Additionally, the amount of HBpin (**3**) could be lowered to two equivalents. Levacher and coworkers reported that the process is highly sensitive to the substrate concentration, and only leads to reproducible yields with concentrations lower than 0.3 to 0.4 mol·L^{-1}. With the optimized reaction conditions, the 2-naphthylpyridine **18** was synthesized from naphthyl triflate **16** and 2-chloropyrimidine **17** in 84% yield (Figure 12) [40].

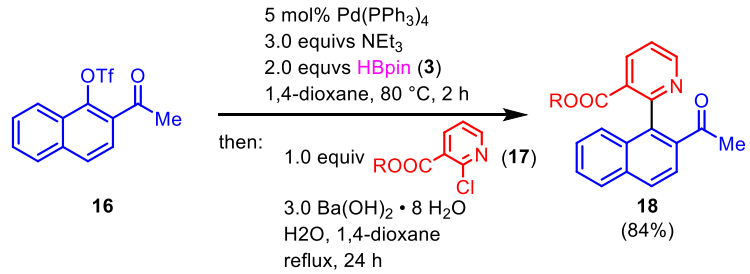


Figure 12. Levacher's one-pot MBSC synthesis of 2-naphthylpyridine **18** [40].

2.4. Colobert's One-Pot MBSC Biaryl Synthesis

Colobert et al. studied the formation of biaryls as precursors for possibly bioactive molecules. The group intensively studied the influence of electron-donating and electron-withdrawing substituents in the *ortho*-, *meta*- and *para*-position of phenyl bromides in the Masuda borylation. They found that electron-releasing-substituted phenyl bromides gave much higher yields than those with electron-withdrawing substituents. These findings match with the data published by the Baudoin group. Colobert used the ligand (oxydi-2,1-phenylene)bis(diphenylphosphane) (DPEphos). With this modified Masuda protocol, the synthesis of unsymmetrically substituted biaryls was approached in a one-pot MBSC sequence. The ligand–catalyst ratio was 2:1. Deviating from the in sensu stricto claim that the initial catalyst source satisfies the complete sequence, for the Suzuki coupling step, a second catalyst loading was necessary. Seven examples with yields ranging from 51 to 90% have been synthesized (Figure 13) [41].

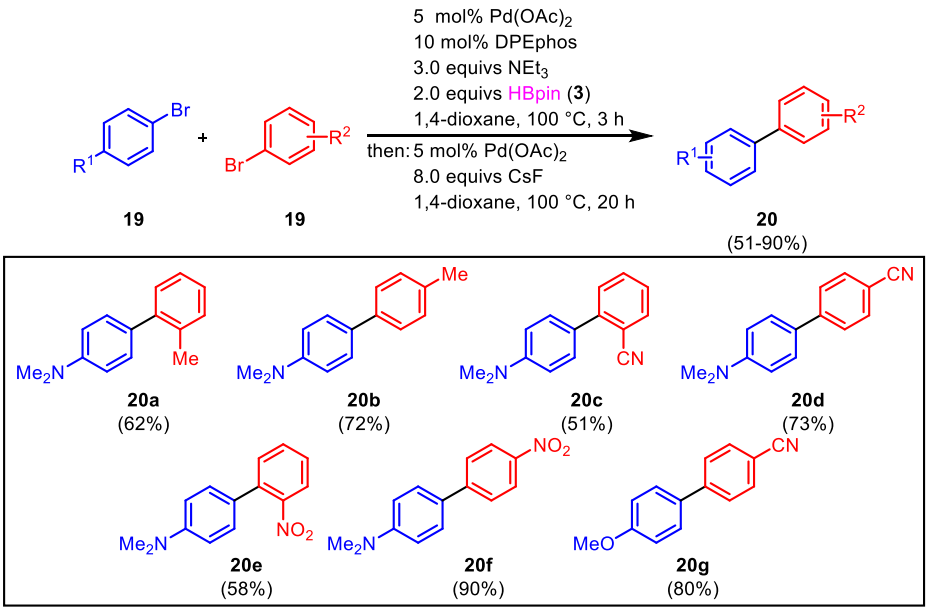


Figure 13. Synthesis of unsymmetrically substituted biaryls **20** via one-pot MBSC sequence by Colobert [41].

2.5. Chai's and Huleatt's One-Pot MBSC Biindole Synthesis

Chai and Huleatt focused on the homo- and hetero-dimerization of sterically congested indoles. To avoid the need to isolate the boronic acid ester intermediates, Chai et al. attempted to perform the dimerization in a one-pot process. For the Masuda borylation step, the group was successful with small loadings of tris(dibenzylideneacetone)dipalladium(0), although the addition of sterically hindered phosphane ligand dicyclohexyl[2′,4′,6′-tris (propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane (XPhos) was required. Additionally, for the Suzuki coupling step, a new catalyst loading was needed. With their MBSC protocol, five examples have been synthesized in yields ranging from 37 to 75% (Figure 14). In the case of compound **23c,** an in situ lactamization occurred to give the pentacyclic compound.

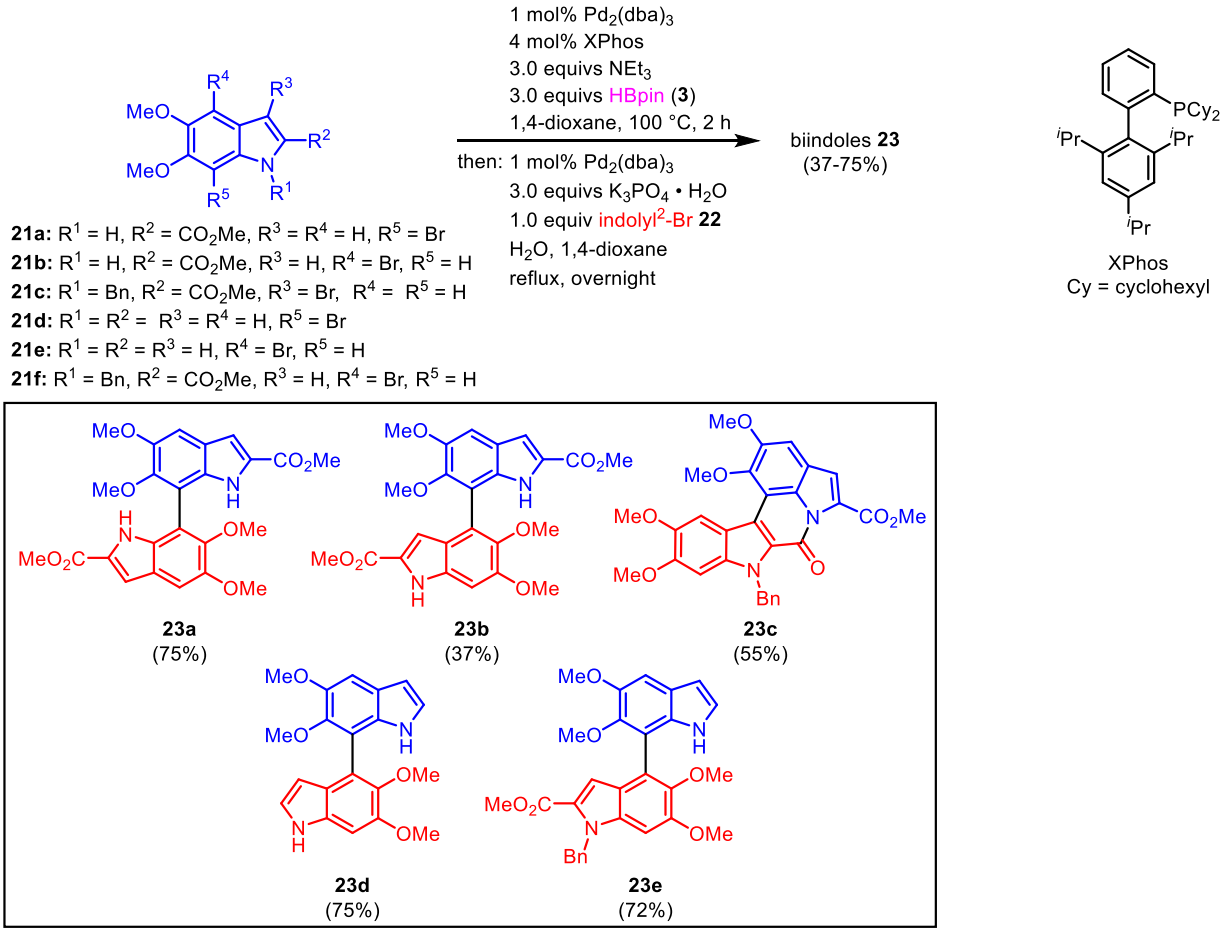


Figure 14. Chai's and Huleatt's one-pot MBSC synthesis of biindoles **23** [42].

2.6. Müller's Generalized One-Pot MBSC Synthesis of bi(hetero)Aryls

Encouraged by successful Masuda borylations of electron-rich bromo phenothiazines in 2002 [43], the Müller group later set out to develop a general MBSC protocol. In 2011, Merkul et al. could improve the MBSC methodology to the efficient coupling of readily available heterocyclic halides with simple catalyst systems and no need for exotic ligands, as previously observed by Levacher [40]. Furthermore, the reaction sequence is performed in the sense of a sequential Pd-catalyzed one-pot process, hence no addition of further catalyst loading is required for the concluding Suzuki coupling step. They envisioned a simple one-pot process to address pharmaceutically promising scaffolds, among them meriolins, which are potent kinase inhibitors [44–47]. Merkul et al. exemplified the tolerance of several functional groups and different six-membered aryl substituents and both hetero iodides and bromides, as well as chlorides, as substrates for the Suzuki step. As the electron-rich component for the Masuda borylation step, *N*-Boc-protected (7-aza)indoles, pyrroles, and

other five-membered ring iodides **24** have been employed. The Boc protection group is cleaved under the Suzuki conditions; therefore, no additional deprotection step is required. Starting from iodides **24**, the Masuda borylation step is performed with low catalyst loading. Then, the heteroaryl halide **25** for the Suzuki coupling step is added in a strictly equimolar loading. In this first publication, 21 examples with yields ranging from 35 to 92% have been synthesized (Figure 15). The general protocol was employed in the concise synthesis of natural product meridianin G (**26i**) and natural product precursor *O*-methyl meridianin A (**26j**). Meridianin A was readily obtained through demethylation [31].

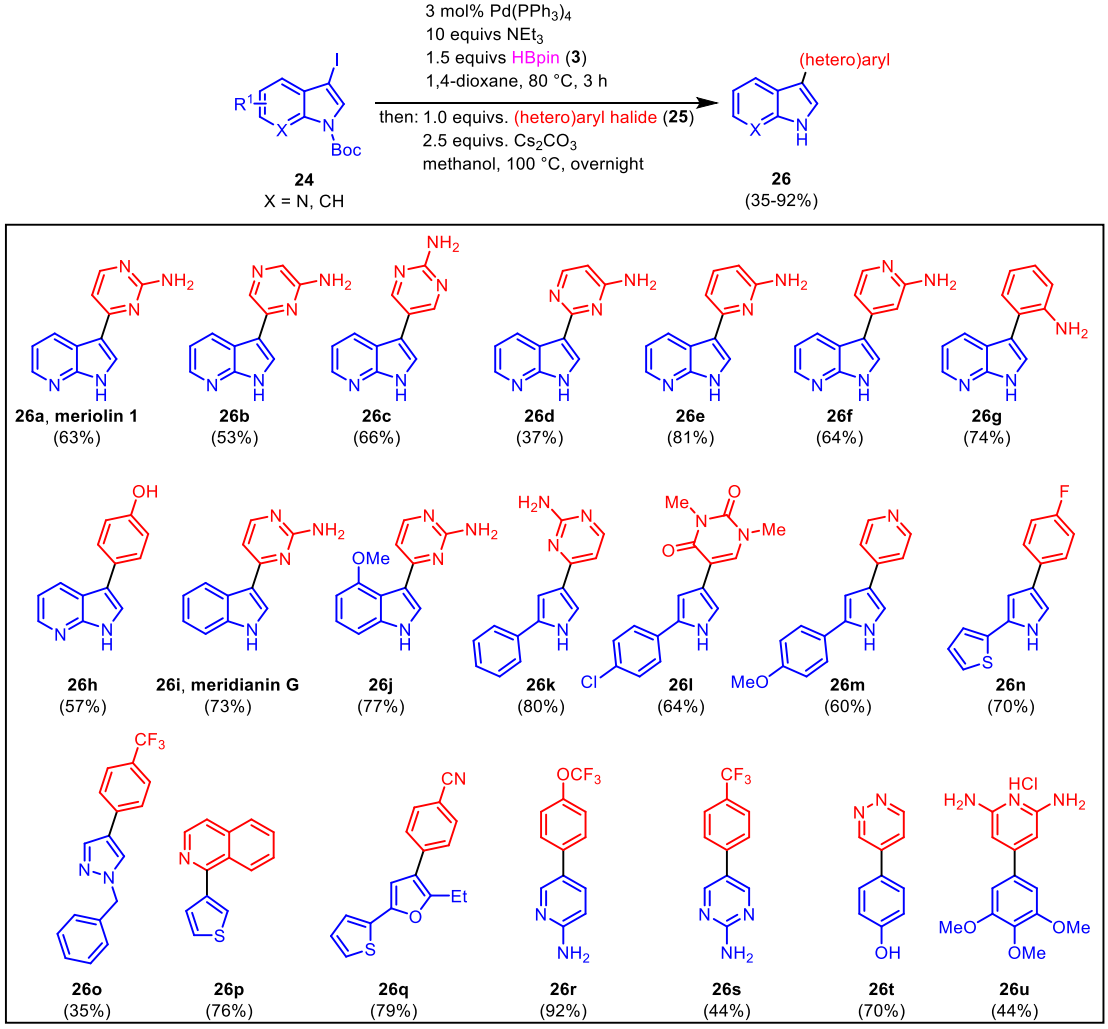


Figure 15. General one-pot MBSC protocol for the coupling of (7-aza)indoles and 5-membered aryl iodides **24** by Merkul et al. [31].

The scope of indole alkaloids **26** synthesized from *N*-Boc-protected indoles was further expanded by Tasch and Sommer (Figure 16) [48,49].

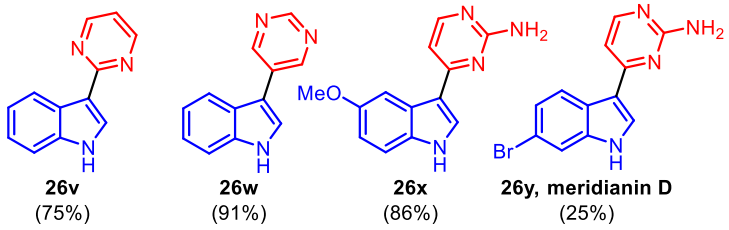


Figure 16. Indole alkaloids **26** synthesized through one-pot MBSC protocol of the Müller group [48,49].

Tasch et al. successfully adapted the general MBSC protocol to approach (di)azine-bridged bisindoles **28** in a pseudo-three-component synthesis. Starting from 3-iodo-substituted indoles **24,** after the Masuda borylation, 0.5 equivalents of the dihalo-substituted heteroaryl **27** are added for the subsequent Suzuki coupling, which furnished the desired bisindoles **28** in yields ranging from 24 to 77% (Figure 17). It was also possible to bridge a 7-azaindole (**28b**) as well as a furane (**28m**) and a pyrrole (**28n**) derivative. Bisindole **28f** is the natural product precursor of *O*,*O*′-methyl hyrtinadine A. The naturally occurring hyrtinadine A was obtained through a subsequent demethylation [48].

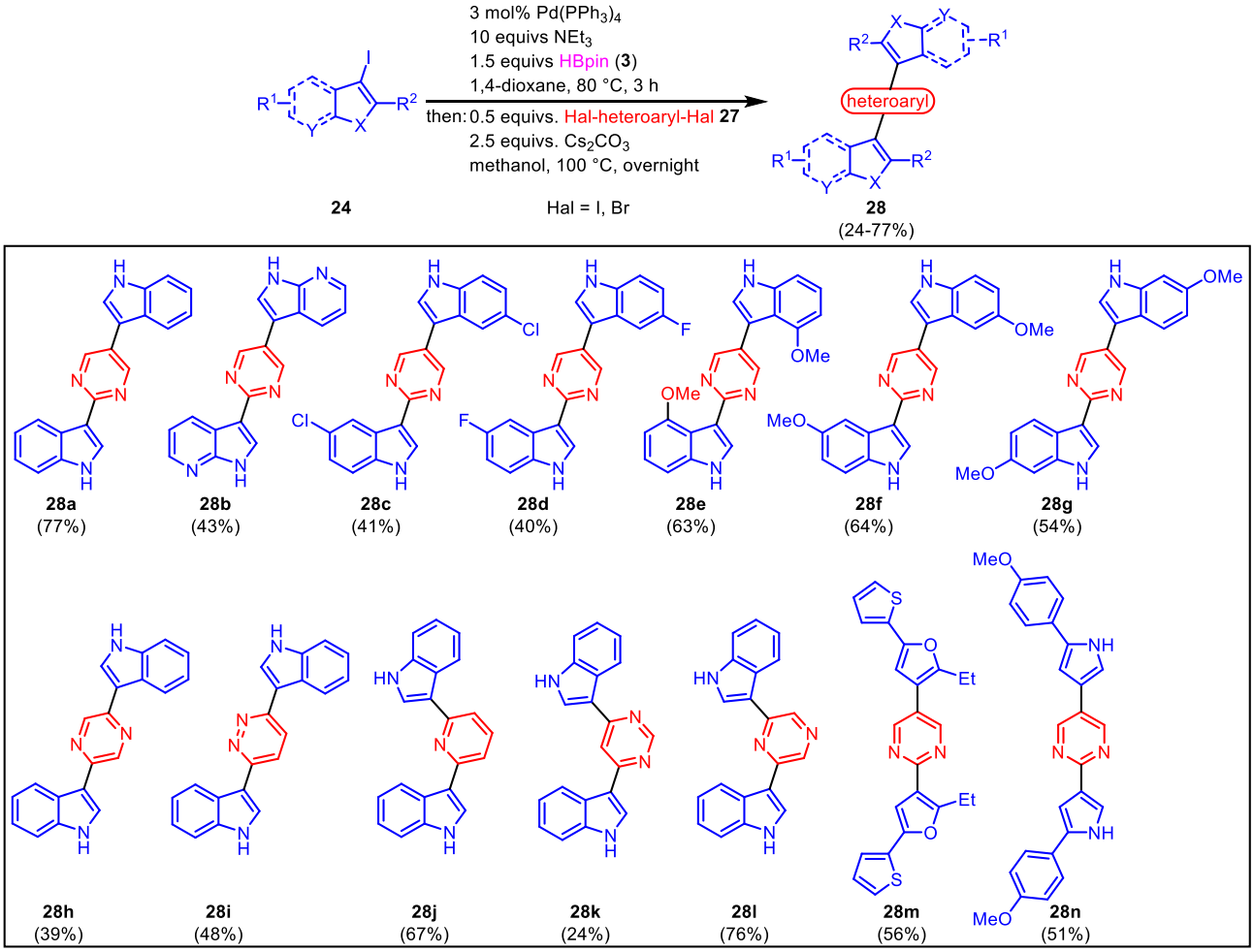


Figure 17. One-pot MBSC synthesis of (di)azine-bridged bisindoles **28** by Tasch et al. [48].

Tasch et al. continued to extend the product scope of the MBSC sequence. The reaction of 5-membered heterocycles as the coupling partner in the Suzuki step appeared to be challenging; the yields were either low or the coupling did not proceed at all under standard conditions. Exchanging cesium carbonate with sodium carbonate, as well as the addition of catalytic amounts of triphenylphosphane to prevent the Pd species from precipitation in the Suzuki coupling, led to higher yields. Additionally, instead of methanol, water was employed as a solvent to improve the solubility of the base. With these optimized conditions, indoles **24** have been reacted with equimolar amounts of bromo thiazoles **29**, which furnished camalexin derivatives **30** in yields ranging from 31 to 75% (Figure 18). In the case of **30i**, the corresponding dibromo thiazole was employed to give the thiazole-bridged bisindole **30i**, an analogue of the biologically active alkaloid nortopsentin. Its isomer could not be isolated; instead, bromo-substituted camalexin derivative **30h** was isolated [50].

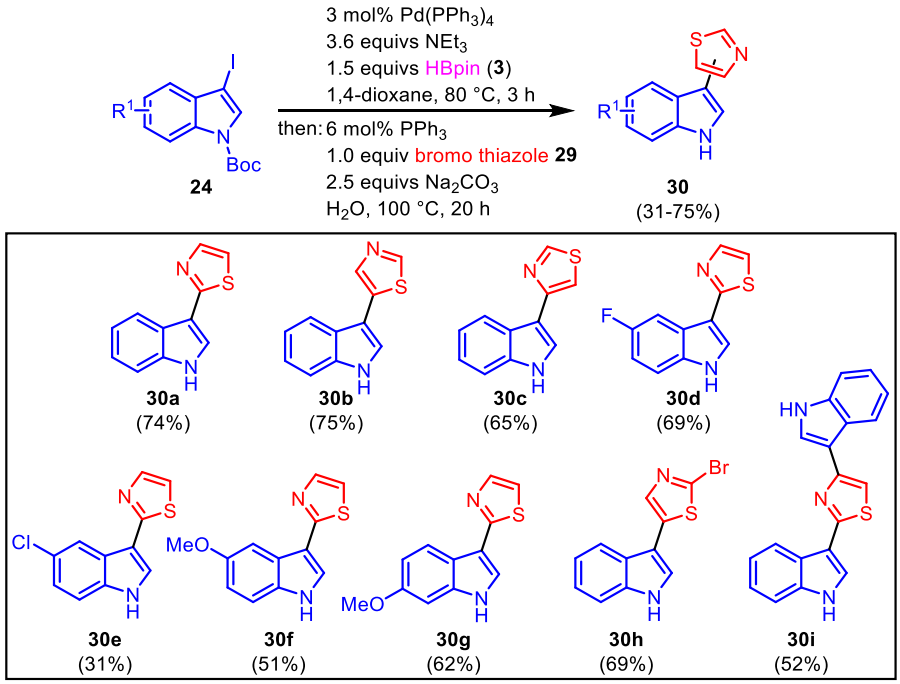


Figure 18. One-pot MBSC synthesis of camalexin derivatives **30** by Tasch et al. [50].

Tasch et al. discovered that, in some cases, the concomitant Boc-cleavage significantly affects the Suzuki coupling, especially if the reaction rate is lower than the base-mediated deprotection. This led to the consideration that the Boc-protecting group should be replaced with the more robust tosyl protection group. A short catalyst screening showed that the standard protocol without the addition of ligands gave the best results. The tosyl-deprotection step could easily be implemented as a third step in the one-pot process. These reaction conditions were employed to synthesize the symmetrically and unsymmetrically substituted 3,3′-biindoles **32** in yields ranging from 33 to 83% (Figure 19).

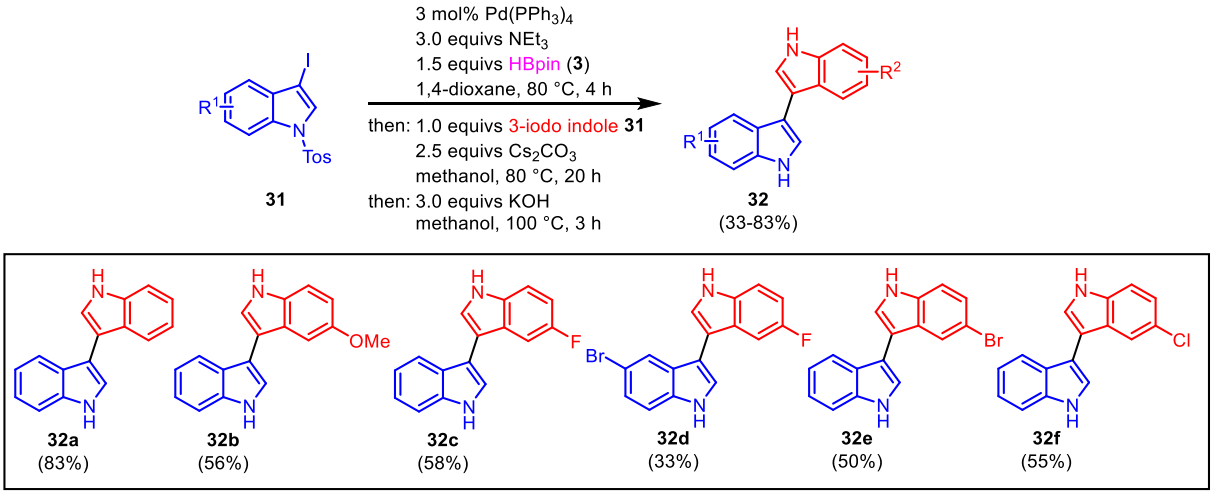


Figure 19. One-pot MBSC synthesis of 3,3′-biindoles **32** by Tasch et al. [50].

The advantages of the more stable tosyl group could be successfully implemented in the standard MBSC protocol. The protection group is stable under Suzuki conditions and can be precisely cleaved in a subsequent deprotection step with a hydroxide base. These adjusted conditions were employed in the synthesis of novel meriolin **26** and bisindole **28** derivatives. The amount of triethylamine was raised to 10 equivalents, which gave favorable results regarding the conversion in the borylation step. The changed protocol still

considers that the Suzuki coupling partner is added in a strictly equimolar manner. Drießen et al. accomplished the synthesis of fifteen meriolin derivatives **26** in yields ranging from 40 to 96% using this novel MBSC protocol (Figure 20). Some derivatives have been identified as promising apoptosis inducers and sphingosine kinase 2 inhibitors [51].

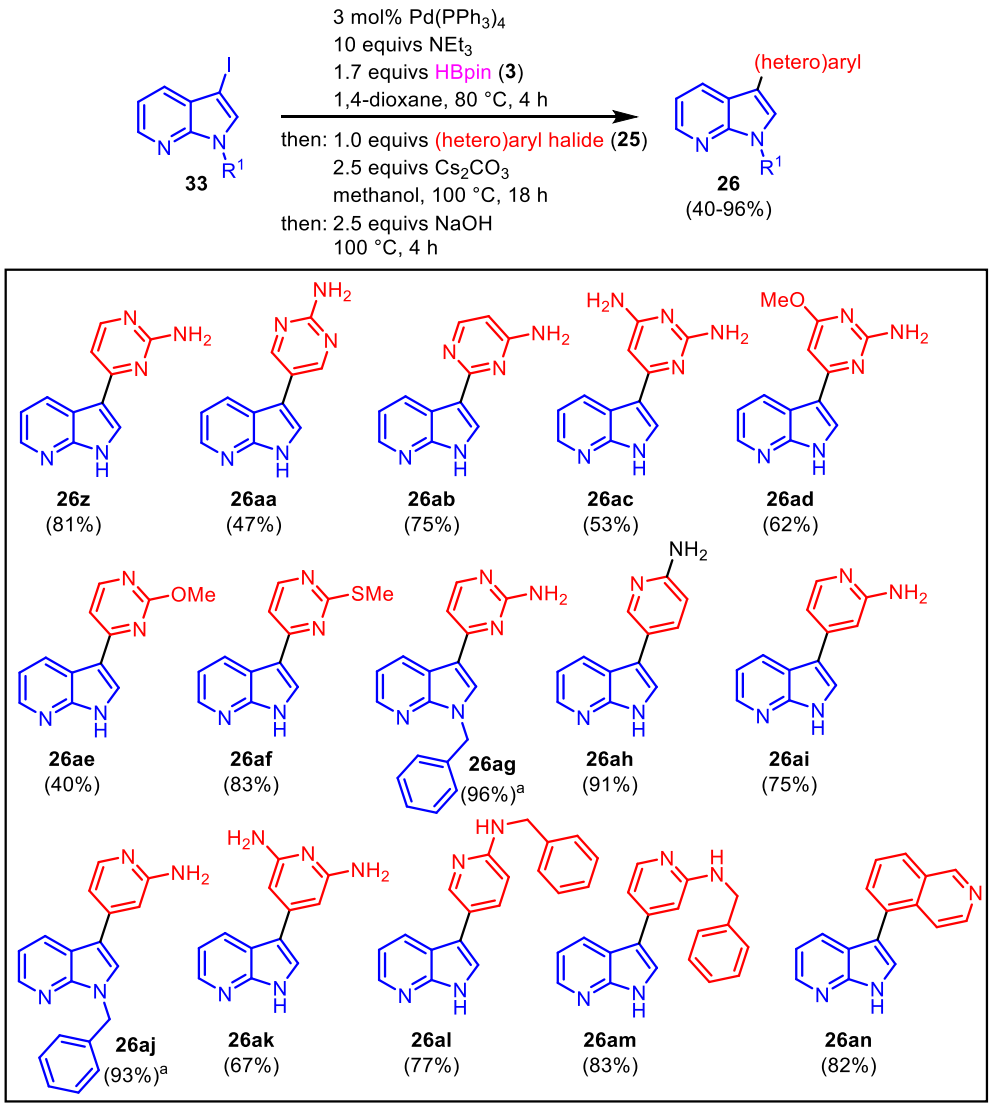


Figure 20. One-pot MBSC synthesis of meriolins **26** by Drießen et al. ([a] Synthesis without deprotection step) [51].

The usage of *N*-tosyl-protected indoles **31** and azaindoles **33** became the standard procedure, as it allows better control of the reaction sequence. Natural products meridianins C (**26ao**), F (**26ap**), and G (**26aq**) have been synthesized using the latter protocol in subsequent publications by Kruppa et al. (Figure 21) [49].

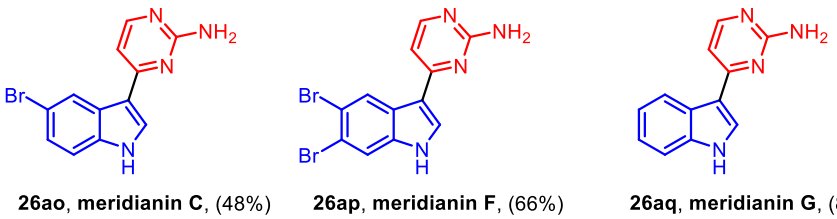


Figure 21. Meridianins **26ao-aq** synthesized through MBSC sequence by Kruppa et al. [49].

The protocol of the pseudo-three-component synthesis of bisindoles **28** has been adapted to *N*-tosyl-protected indoles **31** as well. While the Masuda borylation proceeds similarly to meriolin **26** syntheses, a short optimization study for the Suzuki coupling gave optimal conditions for the synthesis of (di)azine-bridged bisindoles **28**. As a cosolvent, methanol is suitable to give bisindoles in good yields, but the choice of water as a cosolvent not only led to higher yields but also furnished the desired products with higher purity due to less formation of unwanted side products. Additionally, the protocol is suitable for the coupling of dibromo and dichloro (di)azines, which are more readily available than the corresponding diiodides. With the optimized conditions in hand, Sommer, Drießen, and Kruppa synthesized fifteen examples with yields ranging from 39 to 93% (Figure 22). The (di)azine-bridged bisindoles, as well as the derivatives produced by Tasch et al., have been investigated for their antibacterial properties. It was shown that bisindoles **28** with 5,5′-dichloro-substituents display potent antibacterial in vitro and in vivo efficacy against methicillin-resistant *staphylococcus aureus* (MRSA) [52].

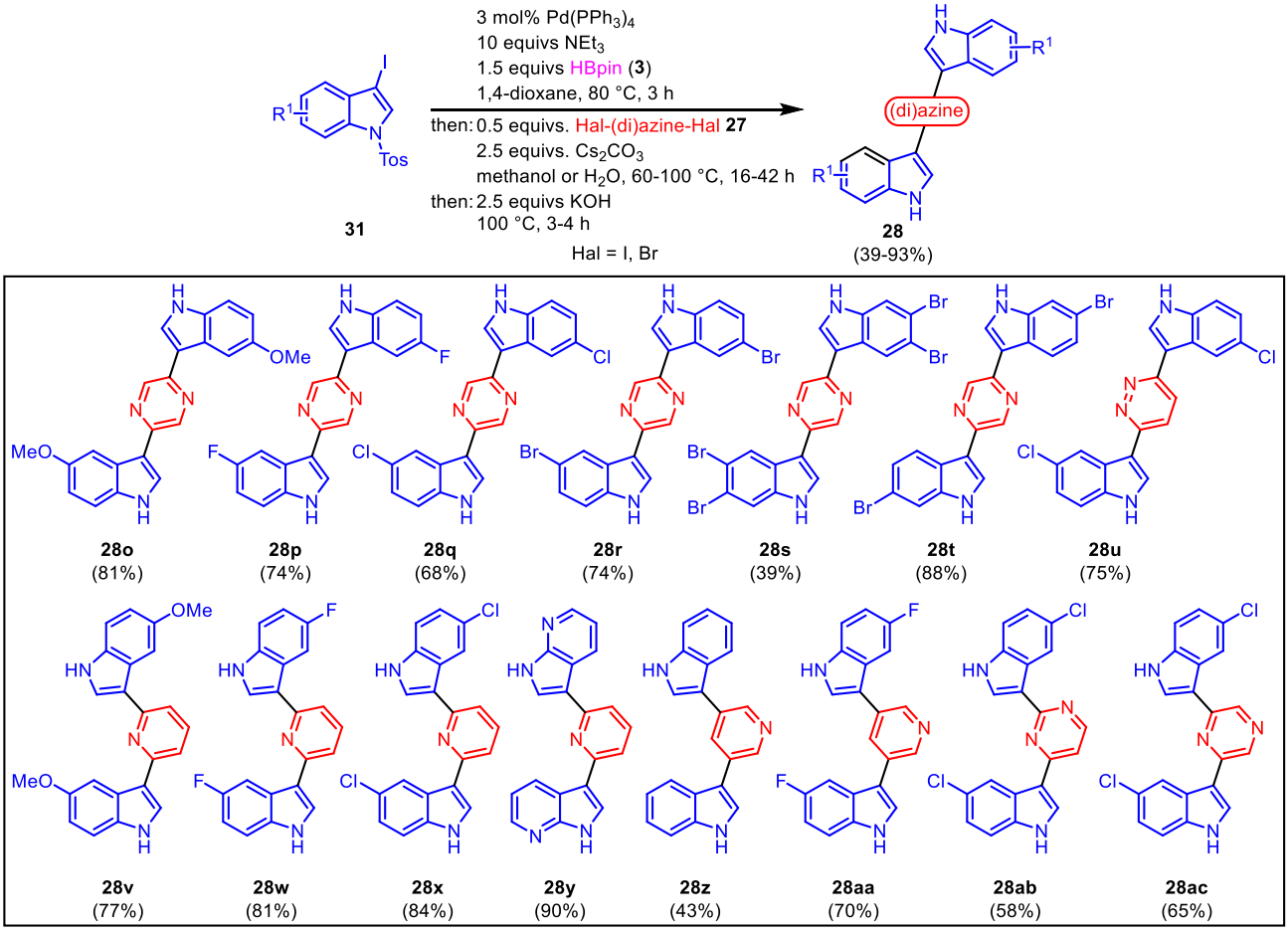
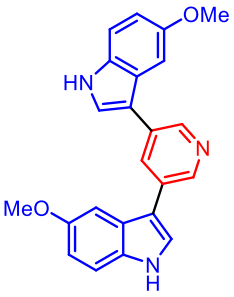


Figure 22. Product scope of the one-pot MBSC synthesis of (di)azine-bridged bisindoles **28** with potent antimicrobial activity against MRSA [52].

This protocol could later be adapted by Kruppa et al. in the synthesis of naturally occurring pyridine-bridged bisindole scalaridine A via the *O*,*O*′-dimethyl precursor **28ad** in 64% yield (Figure 23) [49].

Tasch et al. continued their work to extend the scope of suitable substrates for the MBSC sequence to vinyl halides. After an intense catalyst/ligand screening, the optimized reaction conditions included palladium dichloride as the palladium source, as well as the bisadamantyl-type phosphane ligand cataCXium® AHI by Beller [53]. In this study, the increase in amounts of triethylamine led to lower yields, highlighting the fact that

the Masuda borylation is sensitive to the base concentration, which varies with different compound classes. With the new MBSC protocol, starting from α-bromostyrene (**34**), five examples of α-substituted styrenes **36** have been synthesized in yields ranging from 35 to 83% (Figure 24) [54]. The isolation of other products starting from commercially available vinyl halides was challenging. Consequently, the order of the borylation compound and the coupling compound have been reversed. Starting from aryl halides **35**, after the Masuda borylation, **α**-bromocinnamaldehyde (**37**) was added for the Suzuki coupling, leading to four examples of α-substituted cinnamaldehydes **38** in yields ranging from 56 to 82% (Figure 24) [54].



28ad, *O*,*O*'-dimethyl scalaridine A, (64%)

Figure 23. *O*,*O*′-dimethyl scalaridine A (**28ad**) [49].

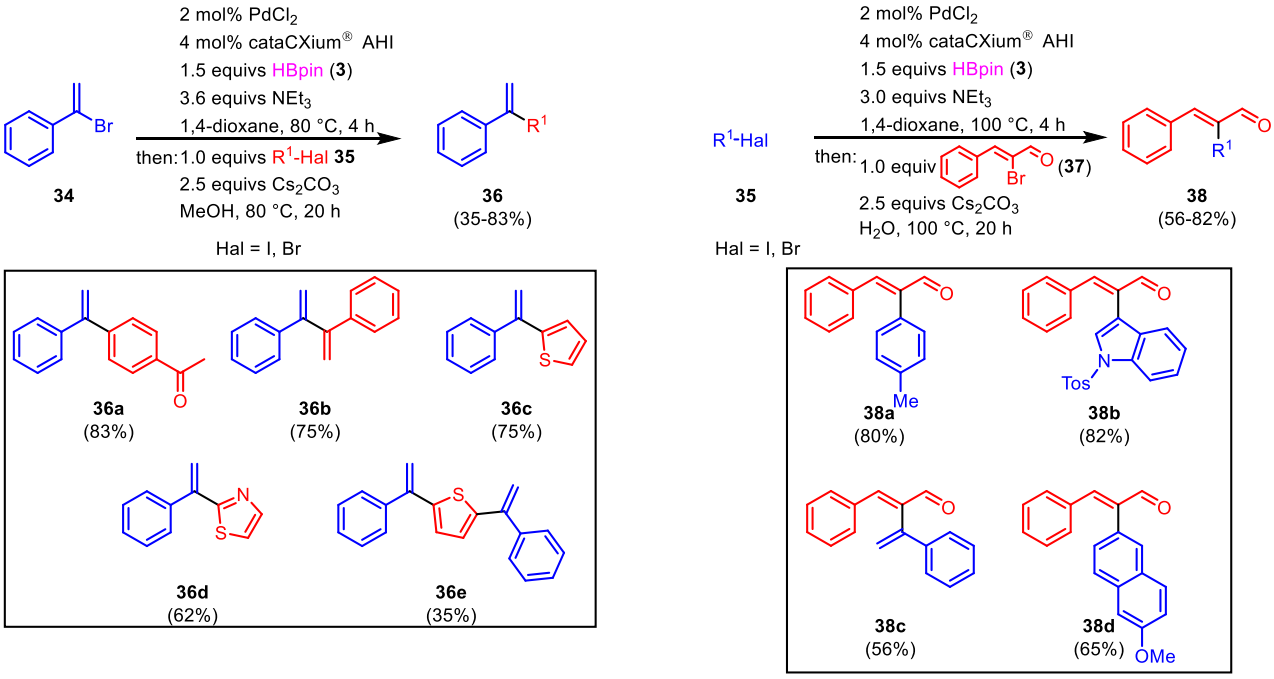


Figure 24. One-pot MBSC synthesis of α-substituted styrenes **36** and α-substituted cinnamaldehydes **38** by Tasch et al. [54].

During the synthesis of cinnamaldehydes **38**, the reactivity of their Michael system is maintained, leading to complex building blocks for further functionalization. Therefore, Tasch et al. envisioned that the sequentially palladium-catalyzed MBSC sequence can be expanded for a concluding cyclocondensation with tosylhydrazine (**39**) leading to a consecutive three-component synthesis of pyrazoles **40**. With this extended sequence, seven 3,4-diaryl 1*H*-pyrazoles **40** have been synthesized in yields ranging from 47 to 82% (Figure 25) [54].

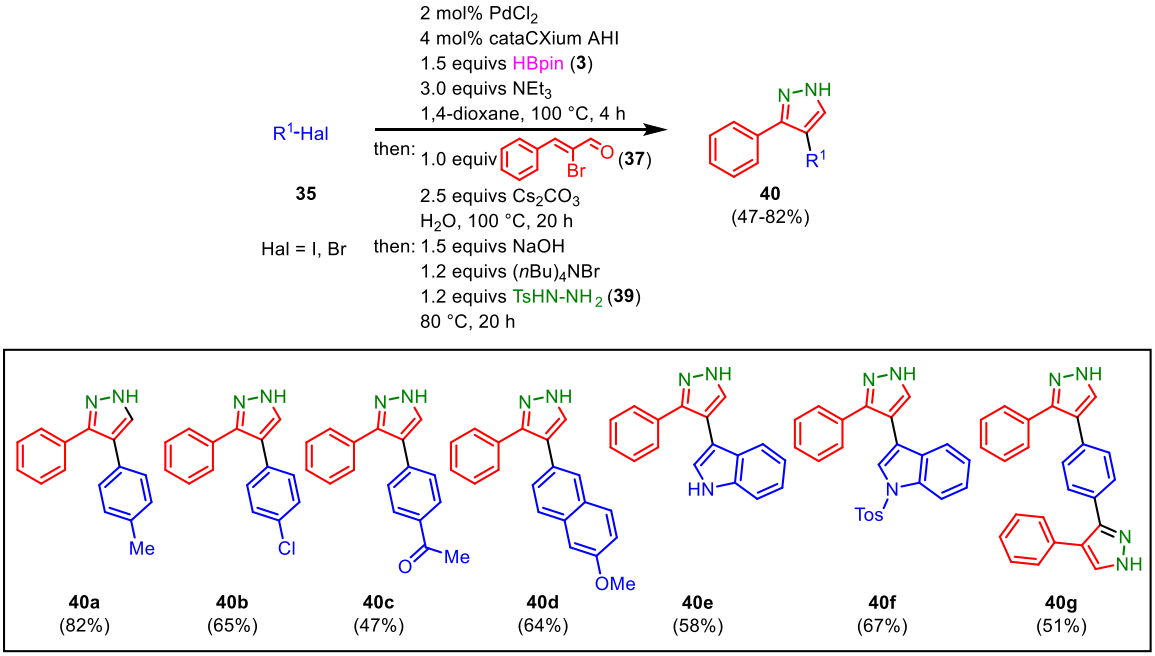


Figure 25. One-pot MBSC sequence as an entry to the consecutive three-component MBSC-cyclocondensation synthesis of 3,4-diaryl 1*H*-pyrazoles **40** [54].

Another possible extension of the MBSC sequence was shown by Drießen et al. The initial MBSC protocol for meriolin derivatives **26** starting from *N*-tosyl-7-azaindoles **33** could successfully be expanded through a Sonogashira reaction, therefore concatenating three sequentially palladium-catalyzed processes—a borylation, a heteroarylation, and an alkynylation. It is noteworthy that only catalytic amounts of copper iodides needed to be added for the concluding Sonogashira coupling, whereas no additional amounts of palladium catalyst or triethylamine were required. To diminish nucleophilic side reactions between the solvent and 2,4-dichloropyrimidine, the solvent was changed from the initial alcoholic carbonate solution (methanol/cesium carbonate) to a mixture of 1,2-dimethoxyethane and water. Aromatic and aliphatic alkynes **42** were employed as Sonogashira coupling partners. This led to fourteen examples of alkynylated meriolin derivatives **43** with yields ranging from 24 to 83% (Figure 26). Selected derivatives have been experimentally and computationally investigated for their photophysical properties [55].

Aside from the synthesis of alkaloids and pharmaceutically relevant scaffolds, the MBSC sequence can be employed in the synthesis of functional dyes. The structure of fluorescent dye **46** was predicted using time-dependent density functional theory (TD-DFT). The *ortho*-methyl group was deduced to create a twisting angle to obtain a small energy gap of the charge transfer states of singlet and triplet characters. The resulting low $\Delta E_{(S1\text{-}T1)}$ should allow for efficient thermally activated delayed fluorescence (TADF). The MBSC sequence gives fast access to the predicted structure, highlighting the building block approach of this one-pot process. The borylation of bromotriarylamine **44** and subsequent Suzuki arylation with 2-iodo terephthalic dinitrile (**45**) furnished the bright blue–green-emitting TADF dye **46** in 50% yield (Figure 27). The different emission mechanisms and corresponding decay times have been extensively studied [56].

In the course of their studies on aroyl-*S*,*N*-ketene acetals (ASNK) with tunable solid-state emission and aggregation-induced aggregation (AIE), Biesen et al. were able to extend their parental system of AIEgens to biphenylene-bridged bisaroyl-*S*,*N*-ketene acetals **48**. For the reaction, the standard MBSC protocol was suitable, though with a slightly higher palladium catalyst loading of 10 mol%. Starting with the bromo ASNK with electron-donating substituents, a Masuda borylation step is performed before the second bromo ASNK is

equimolarly added for the concluding Suzuki coupling step, which furnished twenty examples of bisaroyl-*S*,*N*-ketene acetals **48** in yields ranging from 30 to 98% (Figure 28).

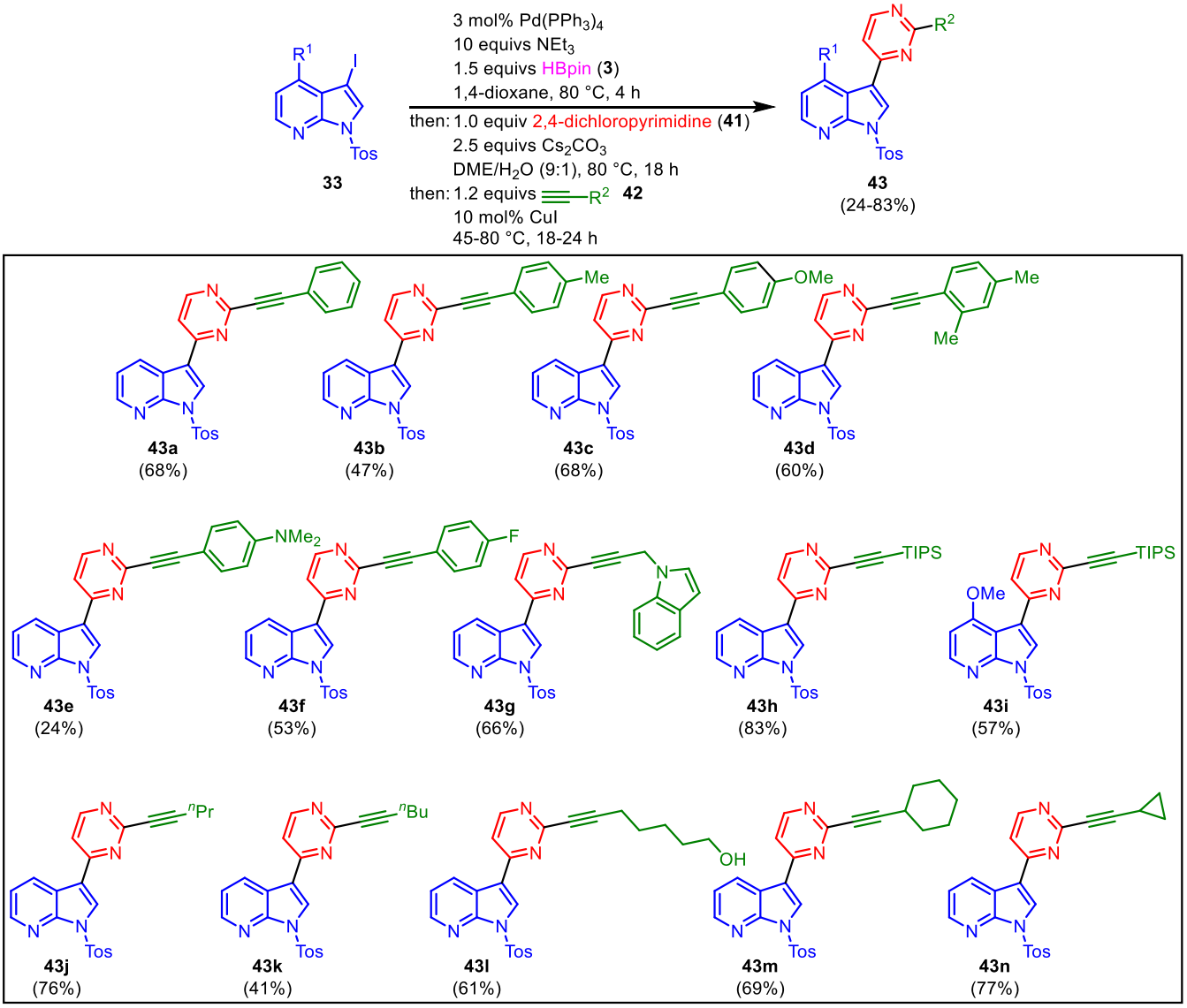


Figure 26. One-pot MBSC initiated three-component MBSC-Sonogashira synthesis of meriolin derivatives **43** by Drießen et al. [55].

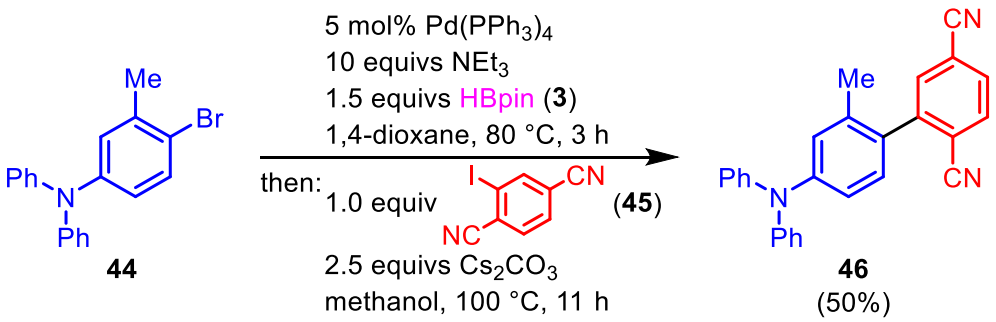


Figure 27. One-pot MBSC synthesis of TADF dye **46** by Sommer et al. [56].

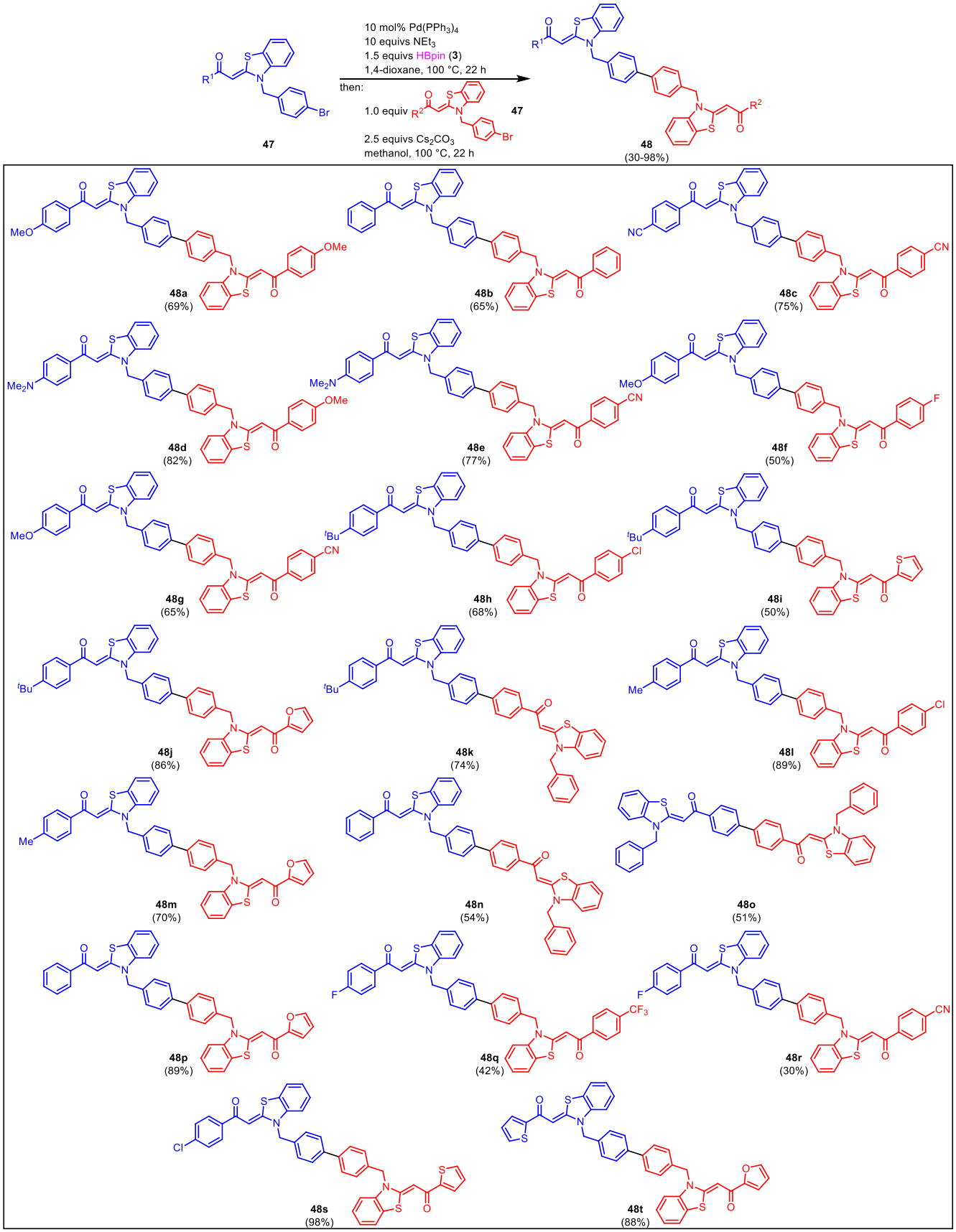


Figure 28. One-pot MBSC synthesis of bisaroyl-*S*,*N*-ketene acetals **48** by Biesen et al. [57].

The sequence tolerates several functional groups. Their solid-state emission colors range from green to red. In contrast to the singular ASNKs, the compounds **48** emitted in ethanolic solutions, therefore posing as aggregation-induced enhanced emission (AIEE) chromophores. A possible application might be as chemical sensors in the determination of water fractions of various alcoholic beverages based on the emission color of the dissolved bisaroyl-*S*,*N*.ketene acetal **48** [57].

To exploit the potential and simplicity of the sequence, Biesen et al. approached the formation of trisaroyl-*S*,*N*-ketene acetal **49**. Starting from toloyl-substituted bromo ASNK **47a,** the MBSC sequence with dibromo ASNK **47b** furnished the desired trimer **49** with a yield of 85% (Figure 29). To ensure full conversion, the amount of catalyst has been adjusted to 20 mol% [57].

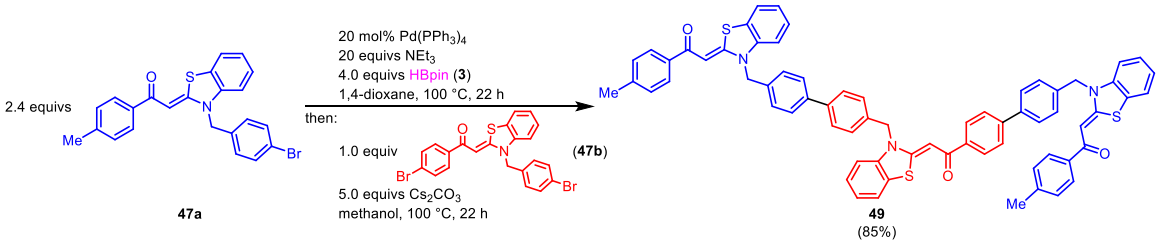


Figure 29. One-pot MBSC synthesis of ASNK trimer **49** via MBSC sequence by Biesen et al. [57].

3. Conclusions

The Masuda borylation–Suzuki coupling sequence is a highly efficient tool for the construction of (hetero)biaryl compounds. The conversion of halogenated (hetero)cycles and vinyl compounds to the corresponding pinacolyl boronic acid esters allows subsequent Suzuki coupling with a second halogenated compound. Therefore, essentially, two halides can directly be connected in a single one-pot process under quite mild conditions (below 100 °C with mild bases). Over the last two decades, the sequence has been intensively studied and continuously improved. From simple biphenyl systems, the need for complex sterically hindered phosphane ligands, or the superstoichiometric use of coupling partners, the one-pot process has been adapted to several compound classes with a general protocol in the sense of a sequentially palladium-catalyzed methodology and the equimolar employment of coupling partners. The influence of substituents, as well as the electronic nature of the substrate, on the reactivity has been determined and confirmed by several groups. The MBSC sequence has been employed for the synthesis of highly active pharmaceutically relevant scaffolds, natural products, and natural product precursors, as well as functional dyes with possible application in modern OLEDs or as chemical sensors. The full potential of the MBSC sequence has yet to be exploited, as it gives fast and elegant access to different compound classes; hence, novel MBSC protocols addressing drugs, dyes, or (hetero)cyclic building blocks can be expected in the future.

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