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Stille vs. Suzuki – cross-coupling for the functionalization of diazocines†

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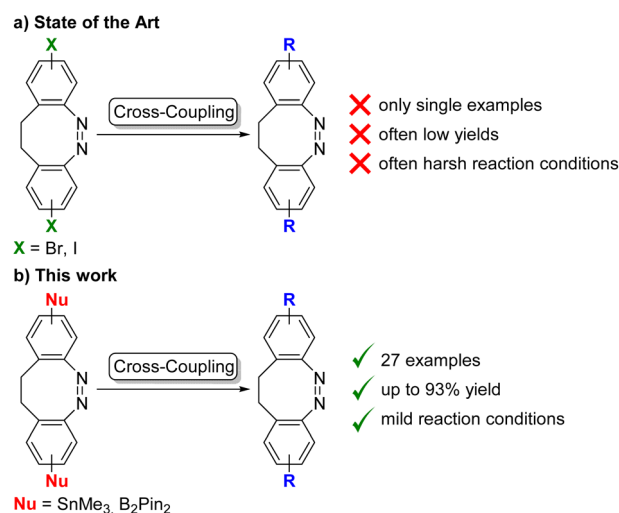
Diazocines are azobenzene derived macrocyclic photoswitches with well resolved photostationary states for the (*E*)- and (*Z*)-isomers, which improves their addressability by light. In this work, effective procedures for the stannylation and borylation of diazocines in different positions are reported. Their use in Stille cross-coupling and Suzuki cross-coupling reactions with organic bromides is demonstrated in yields of 47–94% (Stille cross-coupling) and 0–95% (Suzuki cross-coupling), respectively.

Introduction

In the last few years, ethylene-bridged azobenzenes, diazocines, have garnered interest because of their photochemical properties.¹ The bent (*Z*)-isomer is the thermodynamically favoured state, which can be switched to the stretched (*E*)-configuration using violet light (400 nm). The re-isomerization takes place upon irradiation with green light (520 nm) or thermally. The $n-\pi^*$ absorption maxima of both isomers are well separated, which improves their specific addressability by light.^{1a} Thus, diazocines are promising candidates for a wide range of applications, *e.g.* molecular imaging,² optical data storage^{2b,3} and photodynamic therapy.⁴ They also have been incorporated into functional polymers.^{2a,c,3,5} However, the synthesis of functionalized diazocines is more demanding than of similarly substituted azobenzenes.⁶ Since the discovery of photoswitchable properties of diazocine in 2009,^{1a} the main focus has been on the development of efficient synthetic routes to obtain diazocines with various functional groups.⁶ Several strategies with a broad substrate scope have been published, *e.g.* reduction of dinitro compounds,⁷ oxidation of dianiline derivatives^{4a,8} or a cross-coupling strategy.⁹ With those in hand, the number of accessible diazocines was greatly enhanced: precursors with more complex substitution patterns were used and unsymmetrical diazocines could be obtained.^{4b,10}

However, one common tool in organic chemistry for late-stage functionalization, namely cross-coupling reactions, has only been used sporadically, with diazocine as the formally

electrophilic component.^{4a,8a,11} and one single example with a stannylated diazocine.¹² In those examples, the cross-coupling reactions were not further investigated (Scheme 1a). We were interested in a more general cross-coupling protocol that tolerates a broad variety of functional groups, and which proceeds *via* easily accessible and storable diazocine precursors. They necessitated a high yielding synthesis of stannylated and borylated diazocines, which serve as new synthetic reagents in efficient protocols for Stille and Suzuki cross-coupling reactions. As with azobenzenes,¹³ it is much rarer to be able to prepare the photoswitch as the formally nucleophilic reagent, because of the risk of reduction of the N=N double bond,¹⁴ *e.g.* reductions of the azo group with bis(pinacolato)diboron have been reported.¹⁵ However, if organic bromides can be used as coupling partners, the range of accessible products is much broadened (Scheme 1b).



Scheme 1 Cross-coupling reaction of diazocines.

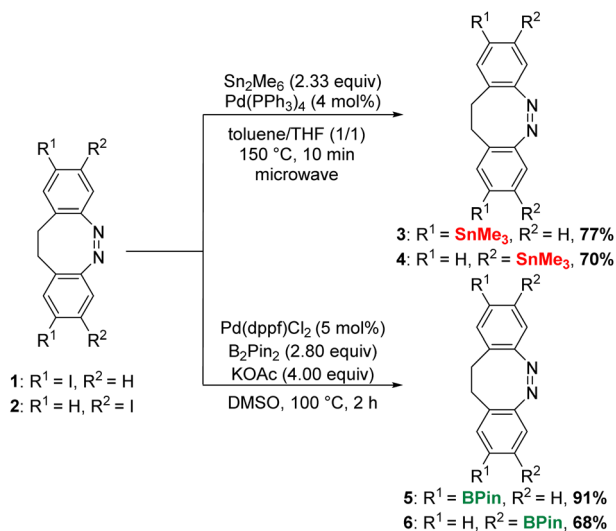
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Scheme 2 Synthesis of stannylated 3–4 and borylated diazocines 5–6.

Results and discussion

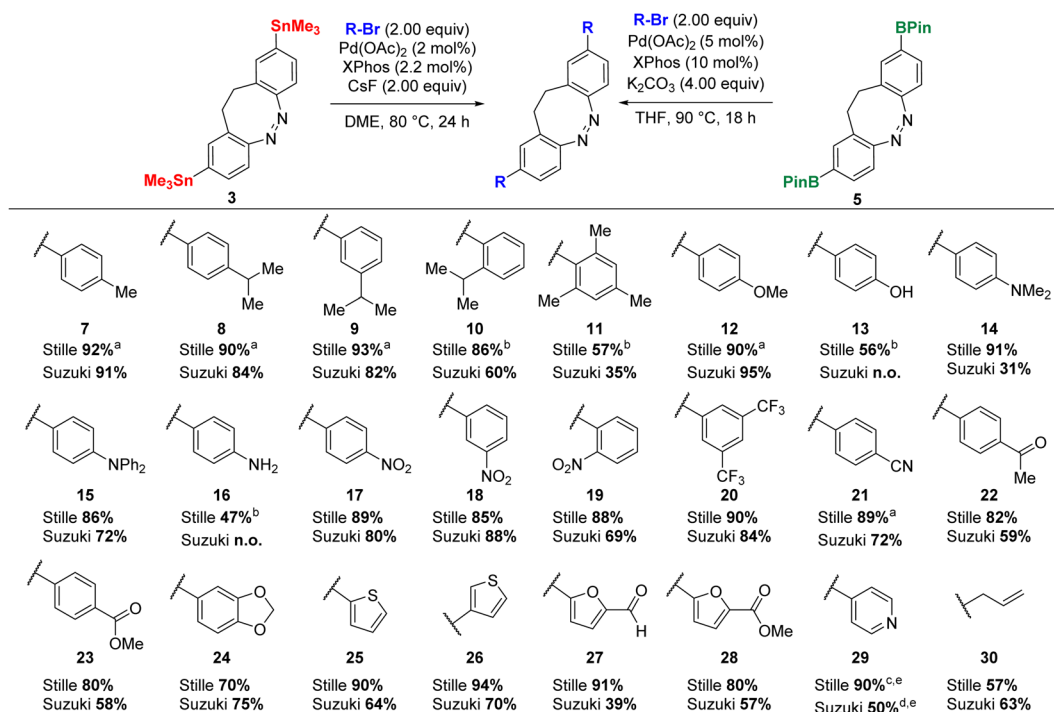
The iodinated diazocines **1** and **2** were synthesized according to optimized literature procedures in yields of 71% and 37%, respectively (see ESI†).^{1a,11g,12} These were to serve as starting materials for the stannylated (**3–4**) or borylated diazocines (**5–6**) as key reagents (Scheme 2). We elected those two types of cross-coupling reaction because of the high bench stability of the corresponding metallated derivatives. Moreover, there was

a high potential for the optimization of the Stille reaction as the reported examples led to very low yields of the cross-coupling (10–31%).^{11b,c,12} To our knowledge, no Suzuki cross-coupling of diazocines has previously been reported.

The stannylated diazocines could be prepared by a microwave assisted Stille–Kelly cross-coupling.^{13a} In this fashion, the coupling of **1** with hexamethyldistannane provided **3** in 77% and the *meta*-derivative **4** was obtained in a similar yield of 70%. In comparison to the previously published *meta*-mono-stannylated diazocine (51%),¹² the efficiency of the cross-coupling procedure was significantly higher.

However, the borylation was less straightforward: to synthesize the borylated precursors **5** and **6** Miyaura borylation was used as the starting point.¹⁶ Unfortunately, this led to the formation of a reduced species in significant amounts (see ESI†). We attempted to suppress the reduction by applying a range of other catalysts, solvents or bases (see ESI†). However, it emerged that to obtain **5** in high yields up to 91%, the reaction time was the most important parameter (Scheme 2). Therefore, monitoring the reaction progress was crucial. Finally, the Miyaura borylation of **2** furnished **6** in a yield of 68%.

With the diazocine derivatives **3–6** in hand, we investigated their ability to serve as the formally nucleophilic coupling partner in Stille and Suzuki cross-coupling reactions (Scheme 3). The Stille reaction required significant optimization efforts regarding the catalytic systems, additives and reaction temperature (see ESI†). Eventually, a modified procedure by Buchwald¹⁷ using a combination of Pd(OAc)₂ and XPhos as catalytic system and CsF as additive proved to be superior in the test reaction of **3** with 4-bromotoluene (92% yield after 4 h).



^a 4 h. ^b Pre-milled Pd(OAc)₂/XPhos (1:3, 10 mol%), 3 d. ^c Pre-milled Pd(OAc)₂/XPhos (1:3, 4 mol%), 1,4-dioxane, 100 °C, 4 d. ^d KOH (2 M).

^e Used as hydrogen chloride. n.o. = not obtained.

Scheme 3 Scope of Stille and Suzuki cross-coupling reactions for *para*-substituted diazocines **3** and **5**.



For the Suzuki cross-coupling, several catalysts and ligands were investigated (see ESI†). We found that the catalytic system involving $\text{Pd}(\text{OAc})_2$ and XPhos also yielded the best result for the Suzuki cross-coupling in the coupling reaction between **5** and 4-bromotoluene (91%).

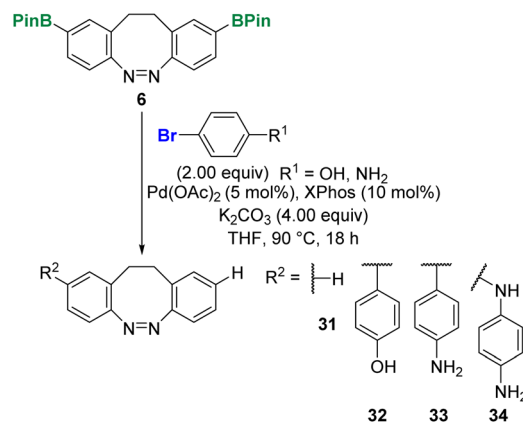
Subsequently, this catalytic system was tested with an electron rich and an electron deficient aromatic electrophile: the coupling of the electron rich 4-bromoanisole performed in a yield of 90% for the Stille coupling and 95% for the Suzuki coupling. The reaction with the electron deficient 1-bromo-4-nitrobenzene yielded **17** in 89% (Stille) and 80% (Suzuki).

Attaching *para*-, *meta*- and *ortho*-isopropyl benzene to obtain **8**, **9** and **10** was possible in high yields except for the Suzuki coupling of 1-bromo-2-isopropylbenzene. In this case, the yield was significantly lower with 60% compared to the Stille coupling reaction with 86%. Steric hindrance seemed to influence the Suzuki cross-coupling more strongly than the Stille cross-coupling. This observation was supported by the synthesis of mesityl-diazocine **11** and *o*-nitrophenyl-diazocine **19**. However, to gain the sterically demanding di-functionalized diazocines **10** and **11** in a sufficient yield *via* the Stille reaction, the amount of catalyst needed to be increased: while the standard reaction conditions mainly led to the mono-coupled diazocines, using 10 mol% of a 1:3 mixture of $\text{Pd}(\text{OAc})_2/\text{XPhos}$ furnished **10** in 86% and **11** in 57% yield. Increasing the catalyst load (up to 20 mol%) for the Suzuki cross-coupling, did not improve the yield of **11**.

Further cross-coupling reactions of electron deficient compounds provided **18**, **20** and **21** in high yields for both cross-coupling types tolerating nitro, nitrile and trifluoromethyl groups. The coupling of stronger coordinating compounds with free electron pairs, *e.g.* aryl aldehyde (**22**), aryl ester (**23**) and furan heterocycles (**27** and **28**), proceeded in low to moderate yields (39–59%) for the Suzuki cross-coupling, while the Stille cross-coupling gave high yields (80–91%). The same trend became apparent upon the coupling of other heterocycles such as thiophenes (**25** and **26**) or pyridine (**29**): the Stille coupling yielded excellent results (90–94%), whereas moderate yields were obtained with the Suzuki coupling (57–66%). However, the functionalization with 4-bromopyridine proved to be challenging for both cross-coupling types.

For the Stille reaction of **3** with 4-bromopyridine it was necessary to increase the temperature to 100 °C and thus the solvent had to be changed to the higher boiling DMSO. For the Suzuki coupling no product could be isolated applying the standard conditions. The desired compound **29** was only obtained with potassium hydroxide a stronger base in aqueous mixture with THF instead of potassium carbonate.

Other electron rich aryl bromides were coupled with **3** and **5** yielding tertiary amines **14** and **15** as well as benzo-dioxole **24** in good to excellent yields. Only compound **14** was isolated in a lower yield of 31% for the Suzuki coupling. Moreover, it was possible to react the unprotected 4-bromophenol and aniline *via* the Stille reaction using 10 mol% of a 1:3 mixture of $\text{Pd}(\text{OAc})_2/\text{XPhos}$. The corresponding diazocines **13** and **16** were obtained in 56% and 47% yield, respectively.



Scheme 4 Side reactions of Suzuki cross-coupling.

For the corresponding Suzuki cross-couplings a multitude of different species was observed (Scheme 4). In both cases, the unsubstituted diazocine **31** was obtained as the main product. Besides the monosubstituted side products **32** and **33**, we could also identify secondary amine **34** as a coupling product with 4-bromoaniline, which suggests a competing Buchwald–Hartwig cross-coupling reaction. In order to solve the problem, we increased the catalyst load to 20 mol% and changed the base (2 M KOH) but neither changing one condition nor changing both at the same time led to the desired products **13** and **16**.

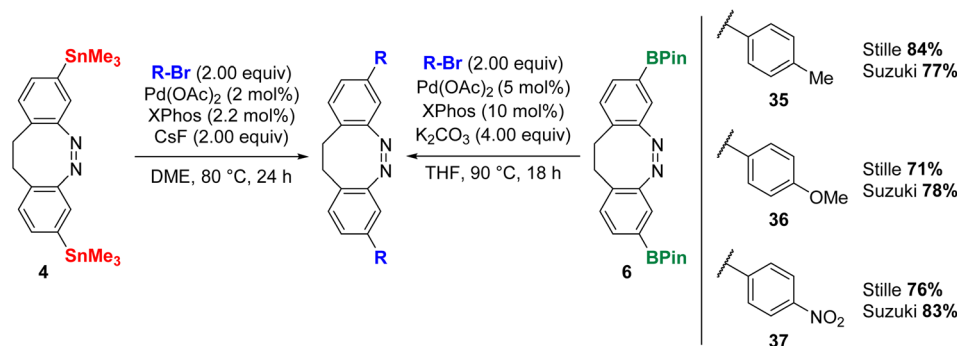
Lastly, it was also possible to react diazocines **3** and **5** with a non-aromatic bromide. Allyl bromide was coupled to yield **30** in 57% (Stille) and 63% (Suzuki), which could be of use as crosslinker for polymerization reactions (Scheme 3).

It was also investigated if the substitution position of the diazocine influences the cross-coupling reactions. In line with the previous test reactions for *para*-substituted diazocines **3** and **5**, 4-bromotoluene, 4-bromoanisole and 1-bromo-4-nitrobenzene were therefore coupled as model substrates with **4** and **6** (Scheme 5). In all cases, good yields were obtained for the Stille (71–84%) and Suzuki coupling (77–83%). In comparison with the corresponding reactions with *para*-substituted diazocines **3** and **5**, the yields were generally lower; *e.g.* the coupling of 4-bromoanisole with *para*-substituted diazocines **3** and **5** proceeded in 90% (Stille) and 95% (Suzuki) but with *meta*-substituted diazocines **4** and **6** in 71% (Stille) and 78% (Suzuki).

Experimental

General procedure for the Stille–Kelly cross-coupling reaction

Under inert conditions, the corresponding di-iodinated diazocine (345 mg, 750 μmol , 1.00 equiv.), hexamethyldistannane (573 mg, 1.75 mmol, 2.33 equiv.) and $[\text{Pd}(\text{PPh}_3)_4]$ (34.8 mg, 30.0 μmol , 4 mol%) were dissolved in toluene (2.5 mL) and THF (2.5 mL) in a microwave reaction vessel. The reaction mixture was stirred for 10 min at 150 °C under microwave irradiation and subsequently filtered through Celite®. Then, the solvent and excess hexamethyldistannane were removed under reduced pressure (9.5×10^{-2} mbar, 80 °C). The residue was purified *via* column chromatography on silica.



Scheme 5 Scope of Stille and Suzuki cross-coupling reactions for *meta*-substituted diazocines 4 and 6.

General procedure for the Miyaura borylation

Under inert conditions, the corresponding di-iodinated diazocine (1.00 equiv.), Pd(dppf)Cl₂ (5 mol%), B₂Pin₂ (2.80 equiv.) and KOAc (4.00 equiv.) were dissolved in DMSO (10 mL mmol⁻¹). The mixture was stirred at 100 °C and the reaction progress was monitored by TLC (cyclohexane/DCM/ethyl acetate 55/40/5). After completion (approx. 2 h), the reaction mixture was diluted with ethyl acetate (20 mL mmol⁻¹) and washed with brine (4 × 50 mL mmol⁻¹). The organic phase was dried over sodium sulfate, filtered and the solvent removed *in vacuo*. The residue was purified by column chromatography on silica (eluent: cyclohexane/DCM/ethyl acetate 55/40/5) to obtain the corresponding diazocine as a yellow solid.

General procedure for Stille cross-coupling reaction

Under inert conditions, the corresponding di-stannylated diazocine (53.4 mg, 100 μmol, 1.00 equiv.), the corresponding brominated coupling partner (200 μmol, 2.00 equiv.), Pd(OAc)₂ (449 μg, 2.00 μmol, 2 mol%), XPhos (1.05 mg, 2.20 μmol, 2.2 mol%) and CsF (30.4 mg, 200 μmol, 2.00 equiv.) were dissolved in dry DME (2 mL) in a pressure reaction vial. The mixture was stirred at 80 °C for 24 h. After cooling to 23 °C, the reaction mixture was filtered through Celite® and the solvent was removed under reduced pressure.

General procedure for Suzuki cross-coupling

Under inert conditions, the corresponding di-borylated diazocine 5 (46.0 mg, 100 μmol, 1.00 equiv.), Pd(OAc)₂ (1.12 mg, 5 μmol, 5 mol%), XPhos (4.77 mg, 10.0 μmol, 10 mol%), K₂CO₃ (69.11 mg, 500 μmol, 5.00 equiv.) and the corresponding brominated coupling partner (200 μmol, 2.00 equiv.) were dissolved in THF (5 mL) and sealed in a pressure reaction vial. The mixture was stirred at 90 °C for 18 h. After cooling to 23 °C, the reaction mixture was filtered through Celite® and the solvent was removed under reduced pressure.

Conclusions

In summary, we developed a robust synthetic methodology to bench-stable bis-stannylated and bis-borylated diazocines in *meta*- and *para*-position to the azo group. These served precursors

for Stille and Suzuki cross-coupling reactions with a broad scope of electrophiles. The catalytic system Pd(OAc)₂/XPhos yielded good to excellent results and tolerated a wide range of functional groups. In this way, functionalized diazocines that might be of interest in material science or biological applications were straight-forward synthesized. While steric hindrance and electron lone pairs lowered the yield, this was observed for the Stille reaction to a smaller extent. Here, the reaction conditions could be easily adapted in order to obtain the desired product in a satisfying yield. Moreover, the coupling of anilines or phenols was possible using the Stille cross-coupling, while Buchwald–Hartwig type side reactions were observed under the Suzuki conditions. Overall, the Stille reaction produced better results in terms of isolated yields and in most cases less catalyst was needed. Nevertheless, other factors besides the yield have to be considered when planning a reaction. In fact, the Stille coupling outperformed the Suzuki coupling applying the here described conditions but the higher potential health risk of the Stille coupling due to the involvement of tin compounds should be mentioned. Depending on the scientific question, the use of the borylated compound for Suzuki coupling reactions might be preferred.

Author contributions

Conceptualization, M. W., W. K. and A. S.; methodology, M. W. and W. K.; validation, M. W., W. K. and A. S.; formal analysis, M. W., W. K. and R. R.; investigation, M. W., W. K. and R. R.; resources, A. S.; data curation, M. W. and W. K.; writing—original draft preparation, M. W. and W. K.; writing—review and editing, M. W., W. K., R. R. and A. S.; visualization, M. W. and W. K.; supervision, A. S.; project administration, A. S.; funding acquisition, A. S. all authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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