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Versatile tuning of *N*-directed palladium C–H halogenation building diversity in *ortho*-substituted *s*-aryltetrazines

Clève D. Mboyi,[‡] Christelle Testa,[‡] Sarah Reeb, Semra Genc, Hélène Cattey, Paul Fleurat-Lessard, Julien Roger, and Jean-Cyrille Hierso*[†]*

Institut de Chimie Moléculaire de l'Université de Bourgogne (ICMUB - UMR CNRS 6302), Université de Bourgogne Franche-Comté (UBFC), 9 avenue Alain Savary, 21078 Dijon Cedex, France

[†]Institut Universitaire de France (IUF), 103 Boulevard Saint Michel, 75005 Paris Cedex, France

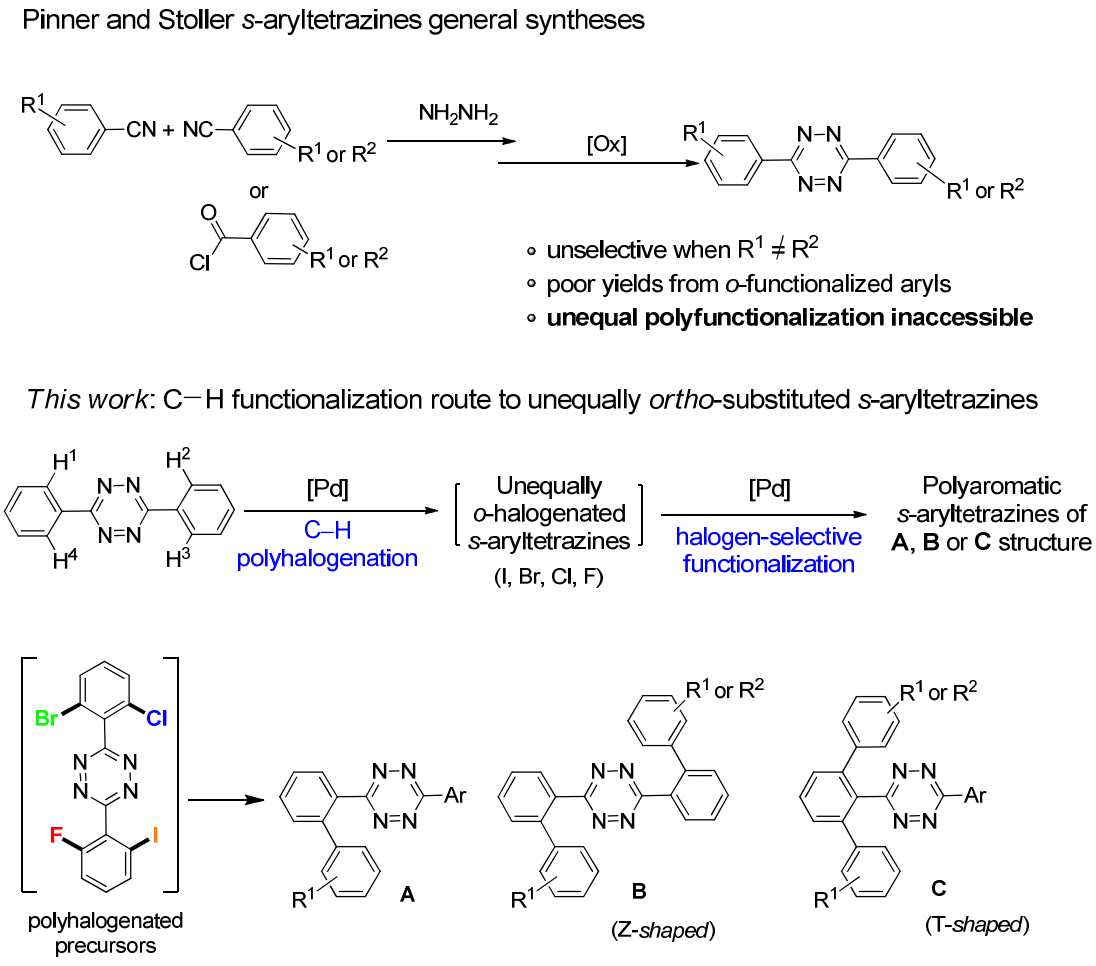
ABSTRACT: We report a general route for synthesizing *ortho*-substituted unsymmetrical biphenyl and polyaromatic *s*-aryltetrazines. These compounds are inaccessible by classical Pinner hydrazine condensation or by the current *s*-aryltetrazine aromatic core functionalization methods described up to now. We exploited multiple versatile *N*-directed palladium C–H activation/halogenation of *s*-aryltetrazine to form C–X bonds (X = I, Br, Cl, F), which collectively produced polyhalogenated unsymmetrical building blocks. We achieved a sequence of selective C–H halogenation reactions in a specific order to produce reactive aryl halides. Polyhalogenated *s*-aryltetrazines can then be used for controlled cross-coupling reactions towards *ortho*-substituted polyaromatic *s*-aryltetrazines. In general, this C–H functionalization route gives access to a large number of variously halogenated building blocks practical for further synthetic implementation of tetrazines (arylation, cycloaddition, etc.). Herein, we exemplified their potential by using halogen-selective Suzuki-Miyaura reactions for divergent construction of novel biphenyl *s*-tetrazines. Therefore, we deliver original poly(hetero)aromatic tetrazine structures, such as new typically "Z-*shaped*" and "T-*shaped*" species. We examined by DFT calculation the origin of the remarkable regioselectivity in some C–H concurrent halogenation reactions. Computations focused at free enthalpy profiles for C–H activation of aryltetrazines to form the intermediate palladacycles by CMD process. We showed that the presence of halogen substituents on aryl groups before further halogenation increases the activation barrier to form the determining C–H activation intermediate palladacycle. XRD studies of functionalized tetrazines evidenced planarity ruptures in the mutual arrangement of aromatic cycles. Finally, this methodology allowed us to deliver a unique tetrahalogenated *s*-aryltetrazine holding not less than four different halogens arranged in *ortho*-aryl positions.

KEYWORDS: halogenation · palladium · C–H activation · tetrazine · polyaromatic · biphenyl

Introduction

s-Tetrazines (1,2,4,5-tetrazines) are the object of considerable current interest in various research fields, which spread out from energetic materials to biomedicine.[1-12] The preparation of tailored *s*-tetrazine allows their implementation via pyridazine formation in inverse electron demand Diels-Alder cycloaddition reactions for bioorthogonal chemistry.[1b, 1e, 1f, 3, 6, 10] As one of the electron-poorer stable heteroaromatic system, *s*-tetrazine has also application in nonlinear optic and fluorescence in the field of addressable sensors and display.[1a, 4, 11] Their high nitrogen content made them also ideal building blocks for explosive materials synthesis in their own,[1c, 2] and as coordinating agent.[1d] Despite this significant extent of applications, the synthetic preparation modes of functionalized *s*-tetrazine remains very limited. They mainly rely on the initial Pinner synthesis of prefunctionalized tetrazine core, which involves a condensation of hydrazines with a nitrile reagent to form an oxidable 1,2- or 1,4-dihydrotetrazine (Scheme 1, top). This synthetic route can give access to aryltetrazines but with serious steric and electronic limitations when polyfunctionalized aryltetrazines are targeted. Post-functionalization of *s*-tetrazine is thus often necessary and clearly lack of precursors. In this purpose, halogenated tetrazines are ideal starting materials, and 3,6-dichloro-1,2,4,5-tetrazine has ubiquitous applications.[1] Recent synthetic progress on *s*-tetrazine post-functionalization includes palladium-catalyzed Heck olefination,[7] and direct sp^2C–H activation/fluorination.[8a] The group of Devaraj disclosed suitable conditions for the synthesis of alkenyl tetrazines from aryl halides and vinyl *s*-tetrazine.[7] We reported that *s*-tetrazine is a particularly suitable group for *N*-directed *ortho*-C–H activation of tethered aryl groups. This allows forming carbon–X bonds (X = O, F) towards mono-, di- and tetra-heterofunctionalized *s*-aryltetrazines[8a-c] such as the commercial acaricidal

fluorinated tetrazines of Clofentezine family.[9] The access to *ortho*-functionalized derivatives is a limitation of classical Pinner and Stoller condensation (Scheme 1) because of steric issues, and other factors such as: (*i*) the availability of aryl precursors, (*ii*) unselective condensation reactions, and (*iii*) the use of hazardous and toxic reagents.[9a,b] *N*-directed metal-catalyzed *ortho*-C–H activation/functionalization proved to be very efficient and delivered for the last decade a variety of directing groups and conditions.[8d-n]



Scheme 1. Preparation of *o*-substituted *s*-aryltetrazines.

Thus, we overcame long-standing limitations attached to *ortho*-substituted *s*-aryltetrazine formation by using palladium-catalyzed straightforward selective C–H halogenation methods.[8a-c]

We present now convenient conditions for versatile multiple unequal C–H halogenation of *s*-aryltetrazines, producing unsymmetrical polyhalogenated building blocks via successive very fast C–H activation/functionalization steps. We achieved a sequence of two or three selective halogenation reactions in a specific order to produce reactive aryl halides, which were used for the controlled synthesis of biphenyl and polyaromatic *s*-aryltetrazines (**A**, **B** and **C** Scheme 1, bottom) with unprecedented structures (*Z-shaped* and T-*shaped*). These polyaromatics optionally include unequally substituted arene moieties. Ultimately, this stepwise controlled C–H functionalization method allowed synthesizing a unique tetrahalogenated *s*-aryltetrazine in which four *ortho*-halogen functions (all different) are present.

RESULTS AND DISCUSSION

Fast rate C–H halogenation. We recently disclosed conditions to achieve selective C–H *ortho*-functionalization that allowed building of mono-, di- and tetrahalogenated homofunctionalized *s*-aryltetrazines.[8a] Noticeable limitations of the methodology was first the several hours reaction time necessary for satisfactory conversion (>15 h), and more importantly the absence of differentiation in the introduced functional groups (halogen, OAc). Building chemically differentiated tetrazines is essential for further use of this block as a versatile and reactive platform for the wide field of applications above-mentioned.[1-12] C–H *ortho*-halogenation may be extended to build unsymmetrical polyfunctionalized *s*-aryltetrazines by using multiple selective halogenation reactions (Figure 1). Further *s*-tetrazines backbone "dissymmetrization" then would be achieved by performing halogen-specific reactions. Because we envisioned a multiple step procedure, we first addressed the limitation in time-efficiency of C–H

halogenation. We investigated microwave conditions for fast electrophilic incorporation of Br, I and Cl atoms.

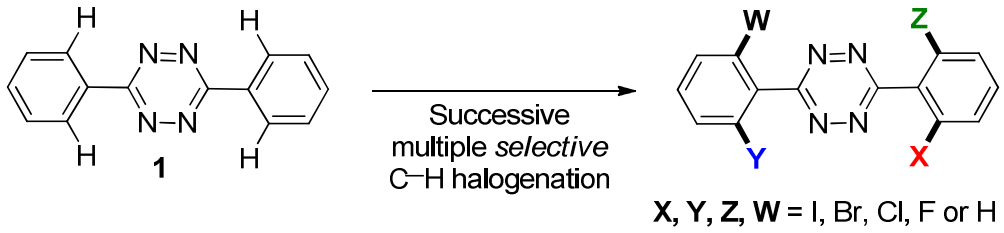
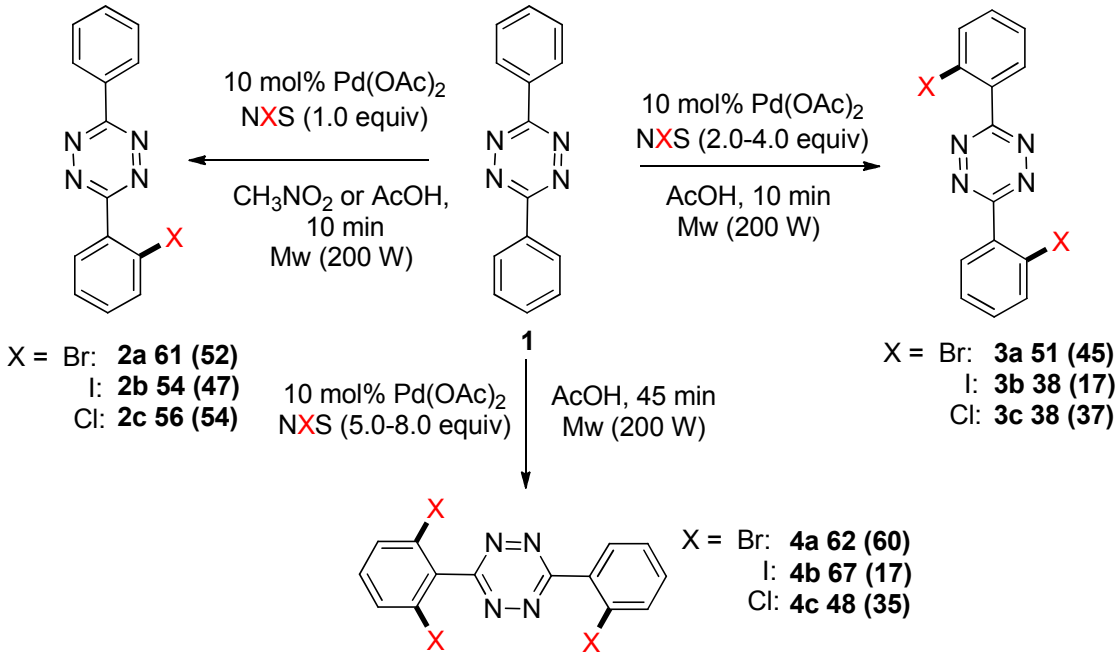


Figure 1. Building of chemically differentiated tetrazines.

We first focused our attention on the selective monobromination of **1** (Scheme 2) with *N*-bromosuccinimide (NBS) as bromination agent, using palladium-catalysis under microwave irradiation (see Supporting Information, Table S1).[13]



Scheme 2. Poly-*ortho*-halogenation of *s*-aryltetrazines at fast rate (isolated yields in brackets)

In the absence of palladium no reaction occurred. For practical reasons we achieved catalytic conditions screening under air. We observed that inert gas conditions are unnecessary for microwave C–H activation/bromination. The reaction using 10 mol% of zerovalent palladium precursors $Pd_2(dba)_3$, and $Pd(dba)_2$, in nitromethane at 100 °C, afforded within 10 minutes the expected 3-(2-bromophenyl)-6-(phenyl)-1,2,4,5-tetrazine (**2a**, Scheme 2) at 58 mg (0.25 mmol scale) with traces of dibrominated 3,6-bis(2-bromophenyl)-1,2,4,5-tetrazine (**3a** < 5 mol%). $Pd(OAc)_2$ precatalyst achieved a better conversion albeit with a lower selectivity (see Supporting Information, Table S1). Compound **2a** was purified and isolated in 52% yield. Other solvents, such as trifluoromethylbenzene, acetic acid or 1,2-dichlorethane led to lower conversions. Under thermal heating conditions,[8a] the optimized catalytic system produced **2a** in 45% yield after 17 h under argon.[14] This protocol employed for selective C–H-monobromination cannot be directly applied to produce monoiodinated and monochlorinated *s*-aryltetrazines, and appropriate conditions need to be tuned from the other *N*-halosuccinimides (see Supporting Information, Tables S2 and S3). The iodinated product **2b** was obtained in 47% isolated yield (see Supporting Information Table S2) and the monochlorinated **2c** in 54% isolated yield (see Supporting Information Table S3) also within 10 min reaction time and satisfactory selectivity (0.25 mmol scale).

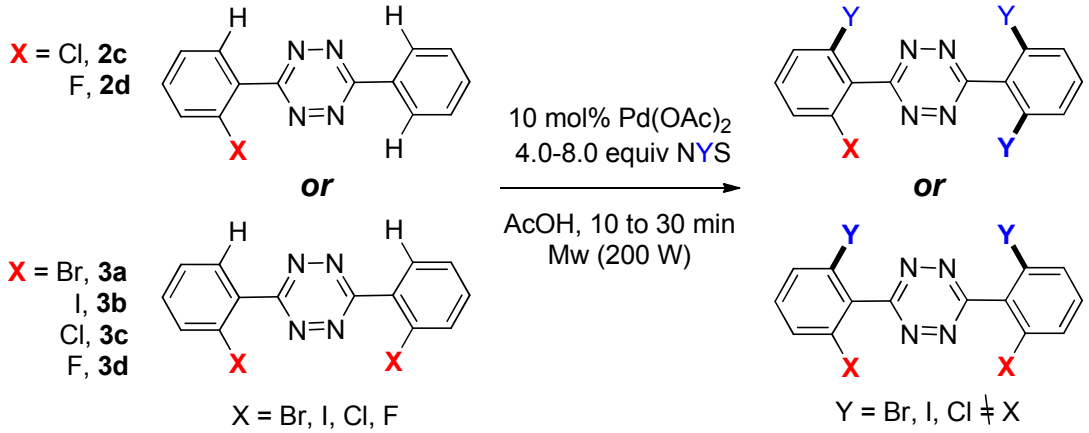
We extended the short-time synthetic access to polyhalogenated *s*-aryltetrazines, including symmetrical *ortho*-dihalogenated **3a-c**. We were also glad to efficiently achieve the synthesis of unsymmetrical *ortho*-trihalogenated **4a-c** (Scheme 2). Dibrominated **3a**, which is a unique precursor for the synthesis of benzo[*a*]acecorannulene bowl-shaped fullerene materials,[9b] was obtained using 2 equiv of *N*-bromosuccinimide (NBS) with $Pd(OAc)_2$ in AcOH at 110 °C in 45% yield (Table S4). Iodinated analogue **3b** was synthetized using a slightly higher temperature of

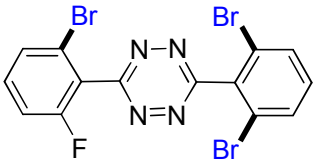
120 °C. However, a significant amount of side products (see Supporting Information, Table S5) including 3-(2,6-diiodophenyl)-6-phenyl-1,2,4,5-tetrazine **3b'** (22%) and **4b** (27%) rendered the isolation of **3b** difficult (17%). Dichlorinated *s*-aryltetrazine **3c** (known as the commercial miticide Clofentezine)[9a] was synthetized in 10 minutes using 4 equiv of *N*-chlorosuccinimide (NCS) at 120 °C, and was isolated pure in 37% yield (see Supporting Information, Table S6). A single step tri-*ortho*-halogenation of **1** (Scheme 2) was achieved from 5.0 to 8.0 equiv of electrophilic halides under 45 min short-time reaction. Tribrominated *s*-aryltetrazine 3-(2,6-dibromophenyl)-6-(2-bromophenyl)-1,2,4,5-tetrazine **4a** was isolated pure in good 60% yield because of a highly selective conversion. Conversely, access to triiodinated *s*-aryltetrazine **4b** was found to be difficult since from a satisfactory 67% conversion of **1**, the product **4b** could be isolated pure in only 17% yield due to its degradation during chromatography. Trichlorinated **4c** was isolated under pure form in 35% yield from a 48% yield conversion. These compounds were ideal precursors for further challenging halogenation procedure that we examined.

Twofold unequal C–H functionalization. Unequally polyhalogenated arenes derivatives would found utility for selectively promoting different functionalization at the aromatic substituent of *s*-tetrazines. Accordingly, we investigated twofold C–H functionalization on variously prehalogenated *s*-tetrazines to reach unequally *ortho*-tetrahalogenated compounds (Table 1). Monofluorinated aryltetrazine **2d** and monochlorinated aryltetrazine **2c** react with *N*-iodosuccinimide (NIS), NBS, or NCS in the presence of $Pd(OAc)_2$ in AcOH at 120 °C to respectively give in 10 to 30 min the unequally tetrahalogenated compounds **5a** (65%), **5b** (67%), **5c** (76%) and **6a** (94%), which were isolated in good to high yield. Compounds **7a**, **7b** and **7c** are easily obtained from the difluorinated *s*-diaryltetrazine 3,6-bis(2-fluorophenyl)-

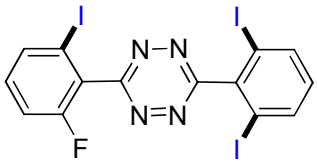
1,2,4,5-tetrazine **3d** and dibrominated, diiodinated and dichlorinated difluoroaryltetrazine were isolated in excellent 86%, 83% and 80% yield, respectively.

Table 1. Unequally tetrahalogenated *s*-aryltetrazine.[a]

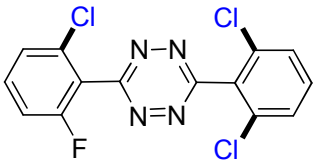




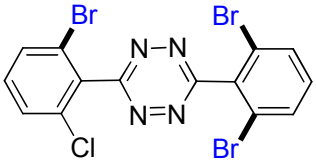
5a, 90% (65)
(NBS = 6.0 eq.)



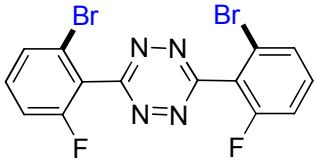
5b, 88% (67)
(NIS = 6.0 eq.)



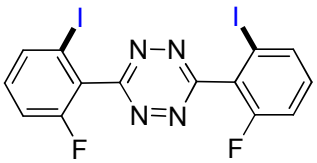
5c, 92% (76)
(NCS = 8.0 eq.)[b]



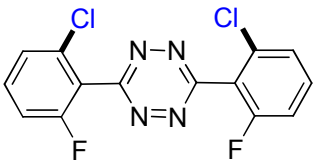
6a, 98% (94)
(NBS = 6.0 eq.)



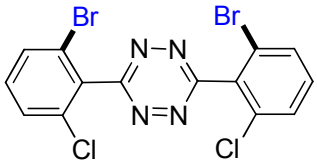
7a, 98% (86)
(NBS = 4.0 eq.)



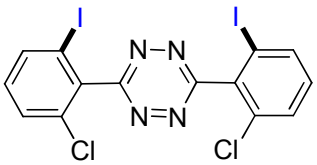
7b, 99% (83)
(NIS = 4.0 eq.)



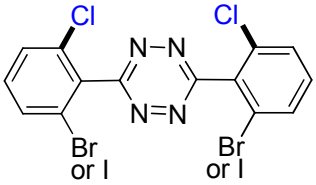
7c, 96% (80)
(NCS = 4.0 eq.)[b]



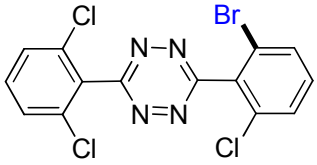
8a, 88% (59)
(NBS = 4.0 eq.)



8b, 99% (83)
(NIS = 6.0 eq.)



9c, mixture
(NCS)



10a, 99% (69)
(NBS = 2.0 eq.)[b]

[a] Conditions: 3,6-diaryl-1,2,4,5-tetrazine derivative (1 equiv), $Pd(OAc)_2$ (10 mol%), [NYS]: NBS, NIS or NCS (4.0 to 8.0 equiv), AcOH (0.125 M), 120 °C, Mw (200 W), under air, 10 min. ^{1}H NMR yield and isolated yield under bracket. [b] 30 min.

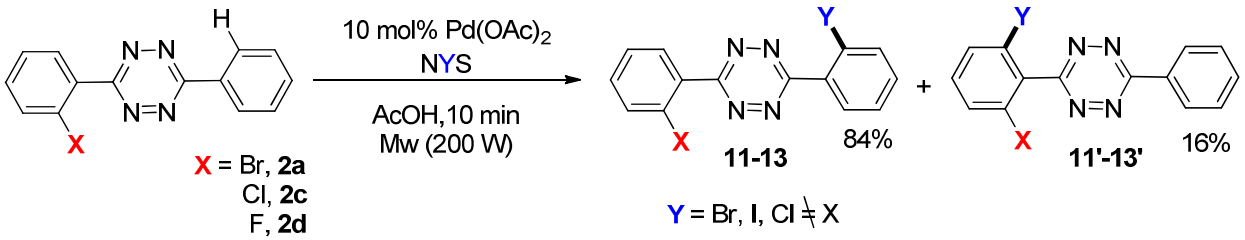
The dichlorinated *s*-aryltetrazine **3c** was used for the introduction of bromide that was achieved with 4 equiv of NBS to reach a conversion of 88% in **8a**. Under such conditions 12% of monobrominated derivative also formed that lowers the isolated yield in **8a** to 59% after workup. Reacting **3c** with 6 equiv of NIS leads to the diiodinated dichloroaryltetrazine **8b** which was isolated in 83% yield.

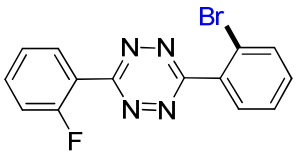
Selectivity in the formation of unequally tetrahalogenated compounds **5a-c** to **8a**,**b** is remarkable since under palladium catalytic conditions additional side-reactions such as dehalogenation or halogen exchange could occur in the course of oxidative addition and reductive elimination reactions involving halides.[15] Accordingly, the double chlorination reactions of the dibromoaryltetrazine **3a** or diiodoaryltetrazine **3b**, using *N*-chlorosuccinimide, led to intractable mixtures of variously halogenated compounds. C–H activation may be kinetically opposed by C–X oxidative addition to low valent palladium (X = Br or I). To overcome this limitation we established an effective halogenation sequence in which is achieved first fluorination and chlorination reactions, before bromide introduction, and finally incorporation of iodine. Such reasoned reaction sequence preserves a high chemoselectivity for C–H functionalization, and thus limits difficult purification processes. Accordingly, monobromination of **4c** was achieved with 2.0 equiv of NBS in 30 min to isolate **10a** in 69% yield (see Supporting Information for XRD analysis details of **10a**). Some of the polyhalogenated compounds reported in Table 1 are patented (or commercial) pest control products, with translaminar and systemic acaricidal, larvicidal and ovicidal effects.[9a,c-e] When

reachable, their tedious syntheses following initial Pinner protocol (Scheme 1) required at least five steps with overall yield below 15%.[9a]

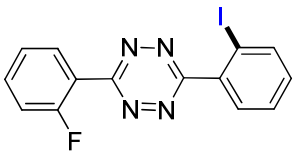
Since we achieved unequal halogenation of the four *ortho*-C–H bond of *s*-aryltetrazine in two simple steps, we then further addressed the more challenging task of unequal selective dihalogenation of *s*-aryltetrazine from monohalogenated *s*-aryltetrazines **2a,c-d** (X = Br, Cl, F, Table 2).

Table 2. Unequally dihalogenated *s*-aryltetrazine.[a]

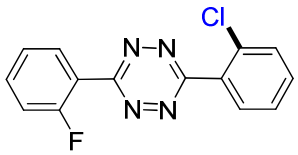




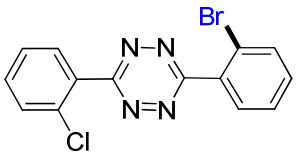
11a, 59% (55)
(NBS = 1.0 eq.)



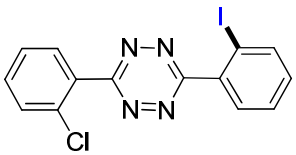
11b, 51% (49)
(NIS = 1.0 eq.)



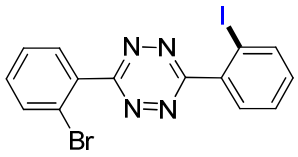
11c, 53% (40)
(NCS = 3.0 eq.)



12a, 67% (53)
(NBS = 1.0 eq.)



12b, 61% (43)
(NIS = 1.0 eq.)



13b, 62% (57)
(NIS = 1.0 eq.)

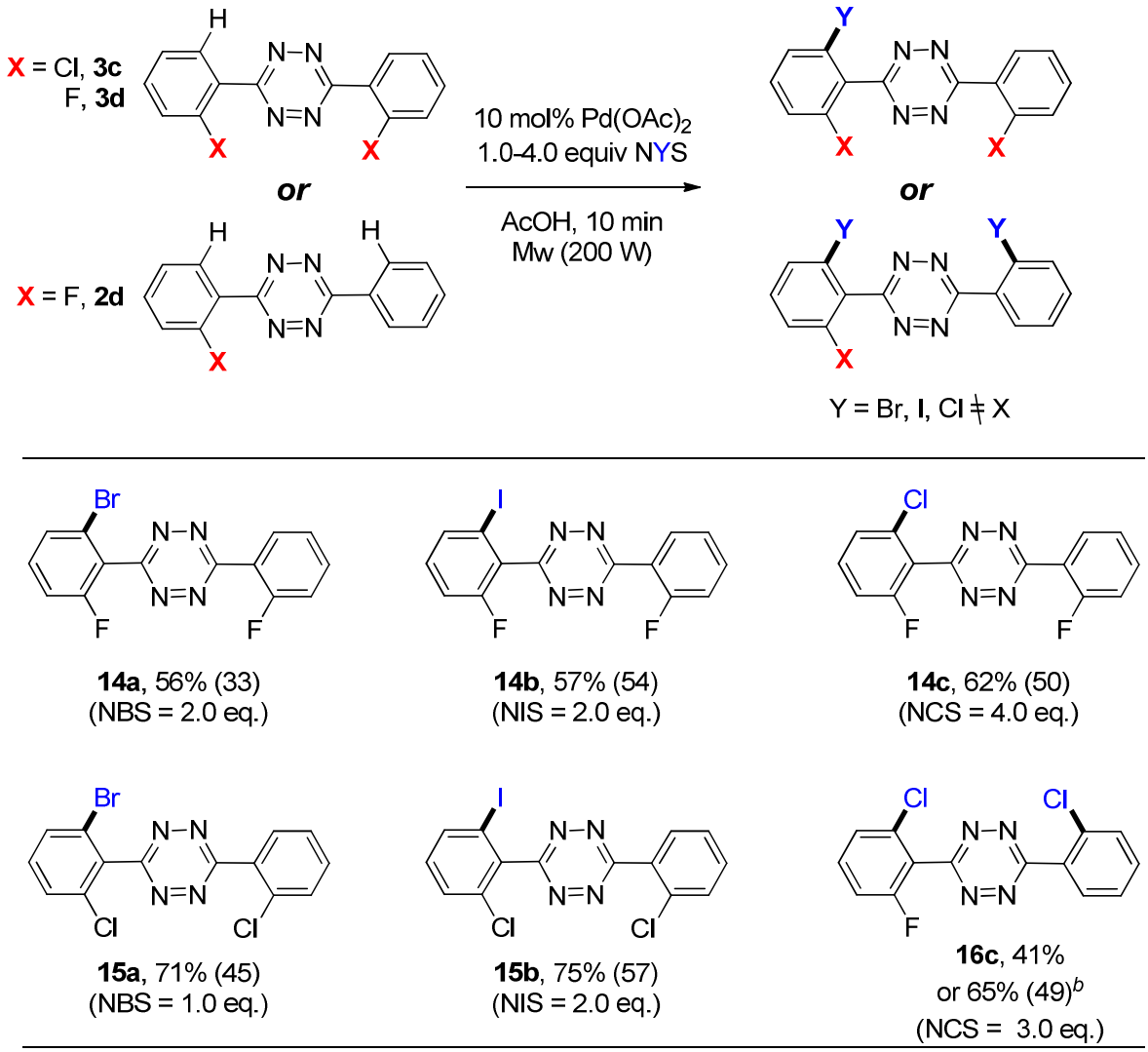
[a] Conditions: 3,6-diaryl-1,2,4,5-tetrazine derivative (1 equiv), $Pd(OAc)_2$ (10 mol%), [NYS]: NBS, NIS or NCS (1.0 to 3.0 equiv), solvent (0.125 M), 120 °C, Mw (200 W), under air, 10 min. ^{1}H NMR yield and isolated yield under bracket.

Using 10 mol% of $Pd(OAc)_2$ in AcOH at 120 °C for 10 min, a single halogenation of **2a, 2c** and **2d** proceeds preferentially on the unsubstituted aryl moiety. This marked selectivity is

apparently not related to the function already present on the aryl (Br, Cl or F) since a ratio of ca. 85:15 for C–H halogenation of ArH *vs* ArX moiety was systematically observed (see Supporting Information, Figure S1 for details). This intriguing situation was further analyzed by DFT calculations (see below). Overall, this two-steps synthetic protocol allowed for the formation of all possible combination of 3,6-bis(2-halophenyl)-1,2,4,5-tetrazine with unequal halides **11a-13b** in ca. 30 to 40% yield. The challenging dihalide **13b** (because of potential trans- and dehalogenation reactions) bearing bromide and iodide functions was even obtained in 62% yield by iodination of **2a** (Table 2). The isomers **11a'-13b'** having two halogens on the same aryl moiety are also isolable, albeit in lower yield (<15%), due to their formation in minor amount.

Unequally trihalogenated *s*-aryltetrazines. We developed a complementary class of unequally trihalogenated *s*-aryltetrazines by adjusting the amount of halogenation reagents used over mono- or dihalogenated *s*-aryltetrazines (Table 3). Monobromination or monoiodination of the difluorinated *s*-aryltetrazine **3d** proceeds selectively in AcOH within 10 min. The halide source stoichiometry needs to be accurately adjusted with an excess of two equiv of *N*-halosuccinimide. The products **14a** and **14b** were respectively isolated in 33% and 54% yield. Selective monochlorination of **3d** is more demanding. Extension of the reaction time –as it was done for the synthesis of **5c** and **7c**– is detrimental to the selectivity, and instead we used four equiv of NCS to isolate **14c** in 50% yield from a selective 62% conversion. Monobromination and monoiodination of the dichlorinated *s*-aryltetrazine **3c** were found to be easier and the trihalogenated products **15a** and **15b** were converted in 71% and 75%. A more challenging, yet accessible, two steps C–H halogenation route to unequal trihalogenated species is the inverse method in which dihalogenation follows monohalogenation of *s*-aryltetrazine.

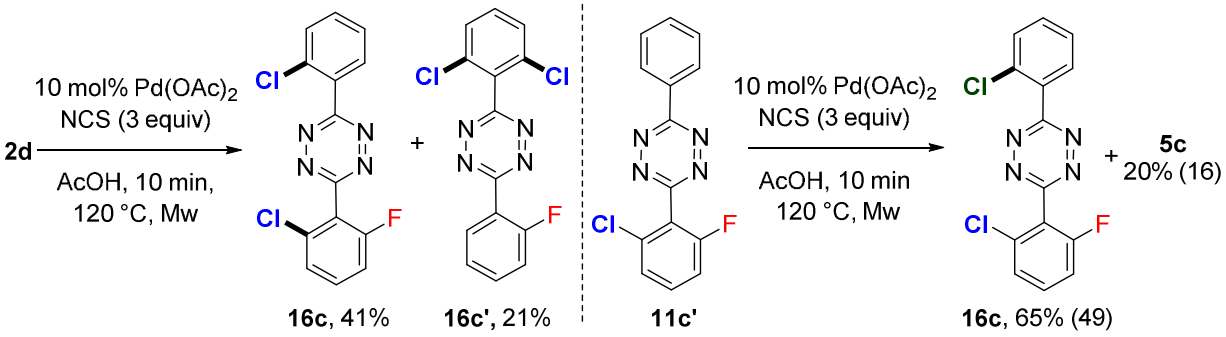
Table 3. Unequally trihalogenated s-aryltetrazines.[a]



[a] Conditions: 3,6-diaryl-1,2,4,5-tetrazine derivative (1 equiv), $Pd(OAc)_2$ (10 mol%), [NYS]: NBS, NIS or NCS (1.0 to 4.0 equiv), solvent (0.125 M), 120 °C, Mw (200 W), under air, 10 min. ^{1}H NMR yield and isolated yield under bracket. [b] See main text for details.

This was achieved for double chlorination of monofluorinated **3d** to yield trihalide **16c** (Table 3). However, isolating **16c** in pure form by this route was not straightforward, and we reconsidered the synthetic strategy (see Supporting Information, Figure S2-S4 for details). Essentially, direct C–H dichlorination of **2d** produces the two isomers **16c** and **16c'** in 67:33

ratio, but in an intractable mixture (Scheme 3, left). Conversely, **16c** is isolated pure in satisfactory yield from the chlorination of **11c'** (Scheme 3, right) that is produced from monochlorination of **2d** (Table 2).

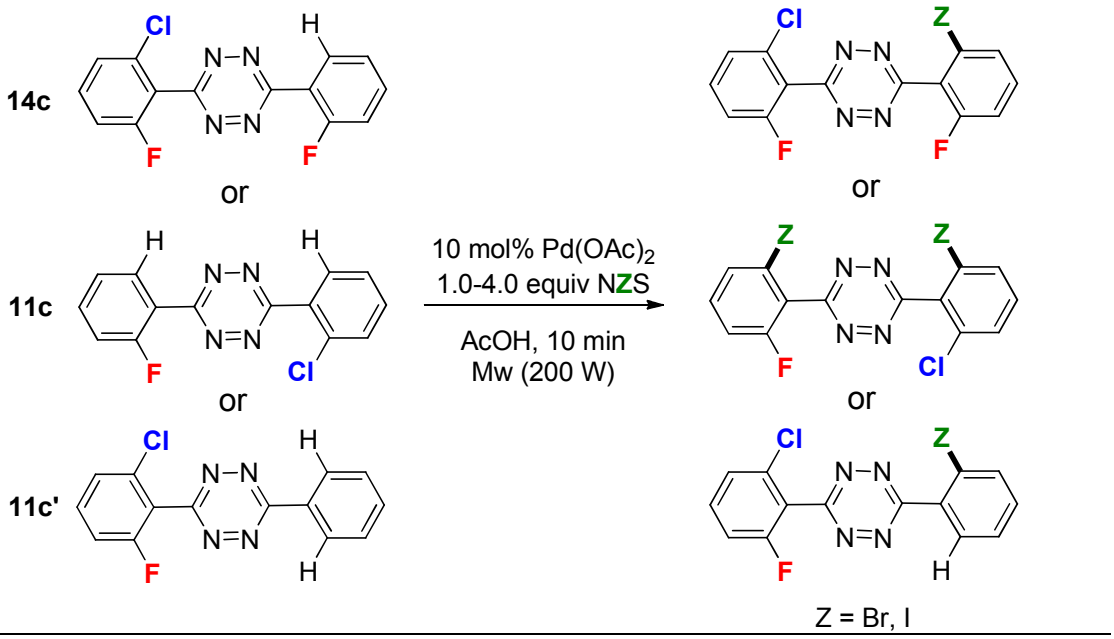


Scheme 3. Concurrent C–H halogenation routes to trihalogenated 16c.

Polyhalogenated *s*-aryltetrazines bearing three or four different functions. To further expand the scope of *N*-directed C–H activation with *s*-aryltetrazines we addressed the challenging synthesis of *ortho*-tetrahalogenated aryltetrazines bearing *three* different halides. We anticipated that such syntheses could be troublesome because Pd-promoted dehalogenation and transhalogenation reactions may lead to intractable mixtures. We investigated two general routes (Table 4), either monohalogenation of unequally trihalogenated compounds (*s*-tetrazine **14c**), or the dihalogenation of unequally disubstituted *s*-aryltetrazines (**11c** and **11c'**). Monobromination of **14c** with 2 equiv of NBS using $Pd(OAc)_2$ in AcOH selectively led to 87% conversion in **17a** within 10 min. After workup the polyhalogenated **17a** bearing a chloride, a bromide and two fluorides was isolated in good 68% yield. Iodination of **14c** in the presence of NIS also allowed getting **17b** in 68% yield. Fast 10 min double C–H bromination and C–H iodination of the compound **11c** was achieved with 4.0 equiv of *N*-halosuccinimide to reach **18a** and **18b** in 70%

and 78% conversion, respectively. These compounds were isolated in ca. 50% and 52% yield respectively after workup.

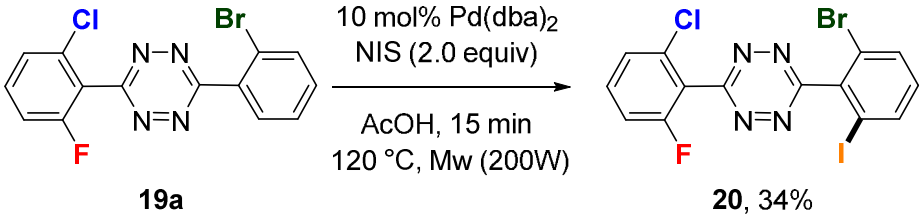
Table 4. Unequally polyhalogenated *s*-aryltetrazine bearing three different halide groups.[a]



[a] Conditions: 3,6-diaryl-1,2,4,5-tetrazine derivative (1 equiv), $Pd(OAc)_2$ (10 mol%), [NZS]: NBS or NIS (1.0 to 4.0 equiv), solvent (0.125 M), 120 °C, Mw (200 W), under air, 10 min. ^{1}H NMR yield and isolated yield under bracket.

In the class of *s*-aryltetrazines holding three different halide functions, we also synthesized **19a**, by monobromination of **11c'** by using one equiv of NBS. This trifunctionalized tetrazine **19a** was isolated pure in 48% yield from a 73% conversion.

Finally, a C–H iodination of **19a** was achieved in the presence of $Pd(dba)_2$ for 15 min and give **20** in 34% isolated yield (Scheme 4, full synthetic scheme is reported (see Supporting Information, Figure S5). This compounds is a rare example of simple organic molecule displaying four different halogen atoms in close proximity.[16]



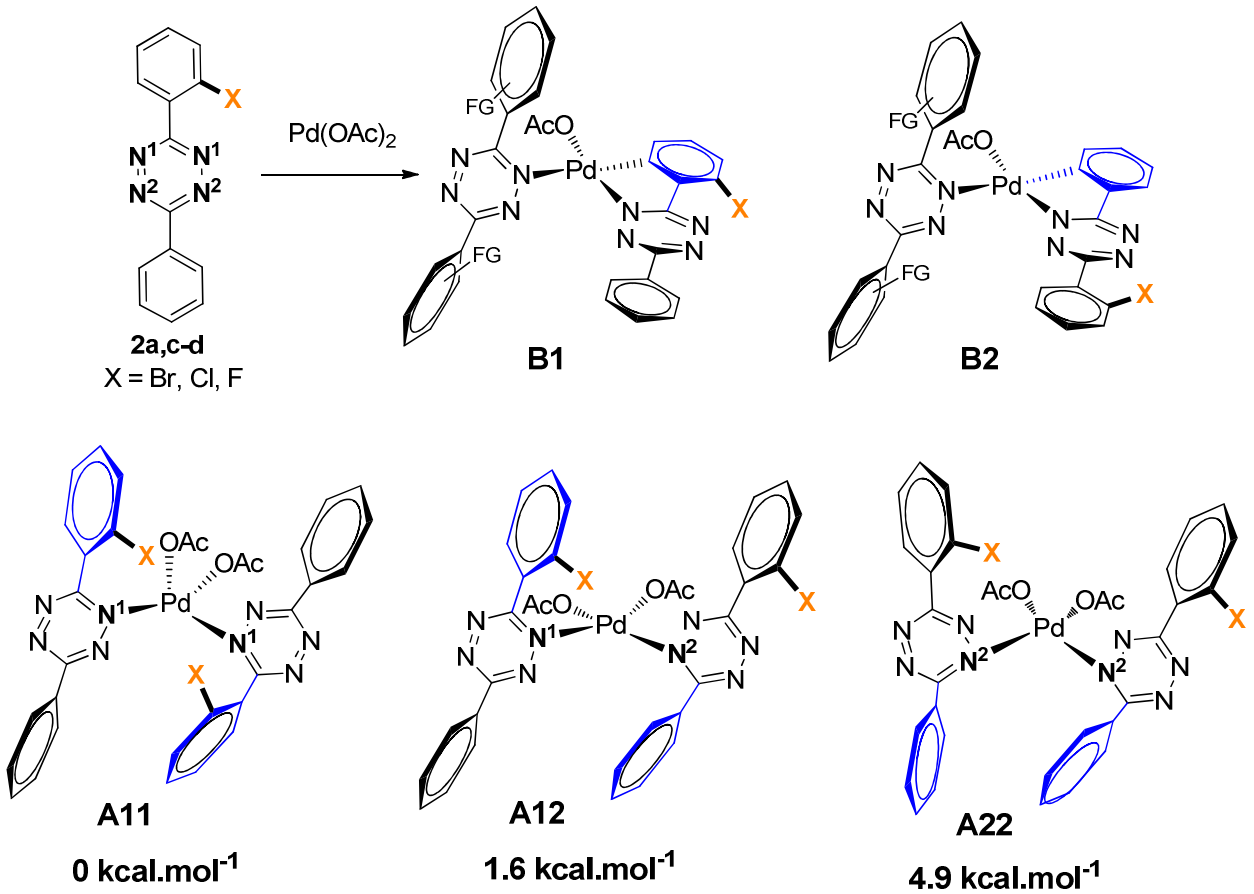
19a **20**, 34%

Scheme 4. Tetrahalogenated *s*-aryltetrazine bearing four different functions.

Selectivity trends in C–H halogenation of monohalogenated *s*-aryltetrazines. Single halogenation of monohalogenated *s*-arylatetrazines **2a,c-d** (Table 2) proceeds preferentially on the unsubstituted aryl moiety whatever the halide function already present on the other aryl (Br, Cl or F). An isomer ratio for the resulting dihalogenated **11-13** and **11'-13'** of ca. 85:15 was systematically obtained (see Supporting Information, Figure S1). To clarify the origin of this selectivity trend the C–H activation step was studied with DFT calculations. Free energies were computed at the ωB97X-D density functional with a basis set of double zeta polarization quality. The acetic acid solvent was modelled using a micro-solvation approach. All molecules were

complexed with one explicit solvent molecule while the bulk effects were described using a continuum (see SI for full computational details).

Mechanistic studies on *N*-directed C–H activation/functionalization have identified the formation of *N*-containing palladacycles as pertinent intermediates in the process.[17] Accordingly, the final selectivity observed in the present case arises from the concurrent formation of the intermediates **B1** and **B2** (Figure 2, top).



[a] Free enthalpies are given for X = F for the precursors complexes

Figure 2. Palladacycles (B) and precursors (A) pertinent in C–H activation of monohalogenated s-aryl-tetrazines.[a]

The collection of dihalogenated aryl tetrazine bis(acetato) Pd(II) complexes **A** (Figure 2, bottom) are pertinent precursors for the formation of **B1** and **B2**. Three isomeric Pd complexes **A11**, **A12** and **A22** which are susceptible of undergoing C–H activation to **B** were computed for X = Br, Cl and F. In these, palladium coordinates a nitrogen atom either in γ-position to the halogen atom ($\mathbf{N^1}$, Figure 2) or in remote δ-position to the halogen atom ($\mathbf{N^2}$). Computation indicates that A**11** is the most stable isomer, however the isomerization barrier is low (20.4 $kcal.mol^{-1}$, see Supporting Information, Scheme S4 for full mechanistic details) and consequently the three isomers co-exist during the reaction. The free enthalpy profiles were computed for the formation of palladacycles **B1** and **B2** from complexes **A** by C–H activation in a concerted metalation-deprotonation mechanism (CMD) assisted by AcOH.[18] Free energies and geometries for the main transition states are given in Figure 3 for X = Br, Cl and F (see Supporting Information for all the structures).

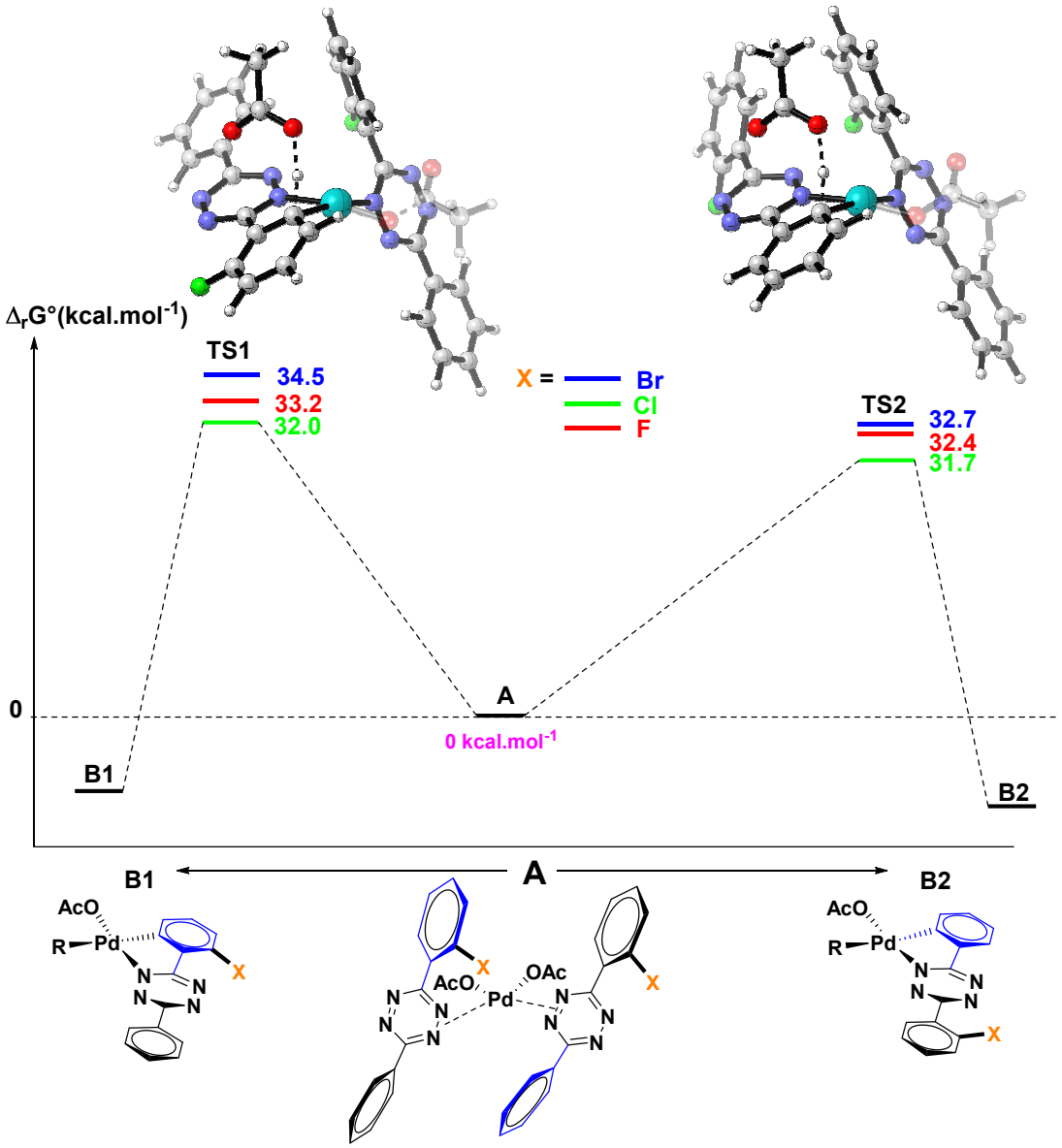


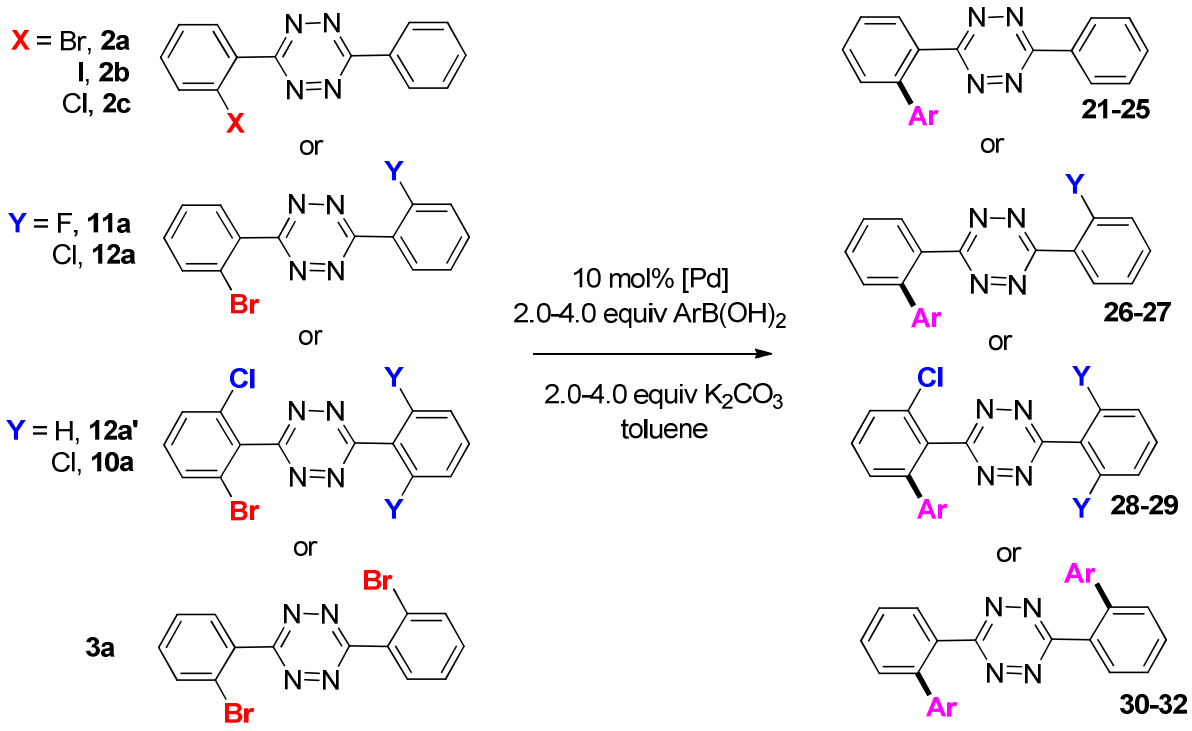
Figure 3. Free enthalpy profiles for C–H activation of *s*-aryltetrazines to form the intermediate palladacycle by concerted metalation-deprotonation mechanism (CMD). Acetic acid solvent was modelled using a micro-solvation approach.

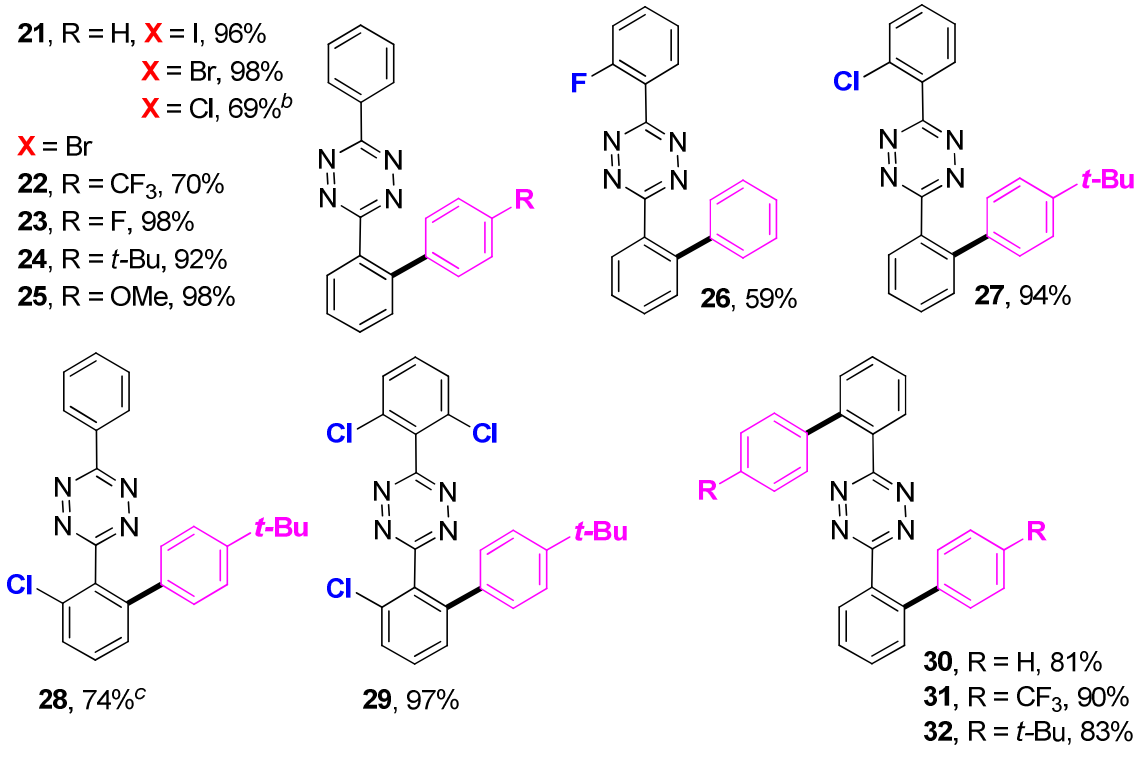
We found lower energy barriers for the C–H activation on the unsubstituted aryl moieties (**B2** formation) with transition structure **TS2** energies ranging from 31.7 kcal.mol^{-1} (X = Cl) to 32.7 kcal.mol^{-1} (X = Br). Halogenated aryl undergoes C–H activation with higher energy, **TS1** ranging from 32.0 kcal.mol^{-1} (X = Cl) to 34.5 kcal.mol^{-1} (X = Br). This trend was common to the three halogenated (**2a**, **2b** and **2d)** we considered. Electron-withdrawing halogen substituents already present on the targeted aryl group before halogenation increase the activation barrier to form the intermediate palladacycle. We already observed this tendency in related *N*-directed C–H activation of functionalized arylpyrazoles.[17d] Consequently, at elevated reaction temperature the halogenation of unsubstituted aryl moiety would be kinetically favored. Under such kinetic control, we calculated selectivity ratio using computed activation free energies (see Supporting Information for full details on the ratio computation). Concerning the fluorinated **2d** (X = F, Figures 2 and 3) the ratio for regioselective second halogenation was found 84:16 identical to average experimental ratio observed for the formation of **11-13**:**11'-13'** (84:16, Table 2, see Supporting Information Figure S1). For chlorinated **2c** we found a consistent ratio of 77:23 for the second halogenation (85:15, see Supporting Information, Figure S1). Calculations from brominated **2a** (X = Br) predict a slightly higher regioselectivity 96:4 compared to experimental results (84:16, see Supporting Information, Figure S1). Globally, these values convincingly reproduced the experimental results.

Halide exploitation for constructing polyaromatic *s*-aryltetrazines – Unsymmetrical structures. We validated the strategy of halogen *ortho*-implantation onto *s*-aryltetrazines by building various unprecedented highly congested polyaromatic biphenyl tetrazine structures. Biphenyl are privileged scaffolds for pharmaceuticals since they bind to a wide range of proteins with high levels of specificity in addition to their recognized anti-rheumatic, analgesic, anti-

inflammatory, antithrombotic and antihypertensive bioactivity.[19] Suzuki-Miyaura palladium catalyzed cross-coupling reactions is known for its high versatility and could be halogen-specific by adjusting the catalytic system. We used $Pd(dba)_2$ in toluene at 110 °C to synthesize the 3-([1,1'-biphenyl]-2-yl)-6-phenyl-1,2,4,5-tetrazines **21**-**25** in excellent yields (70% to 98%, Table 5).

Table 5. Polyaromatic biphenyl tetrazines from one step construction.[a]





[a] Conditions: tetrazine derivative (1 equiv), $Pd(dba)_2$ (10 mol%), aryl boronic acid (2.0 or 4.0 equiv), K_2CO_3 (2.0 or 4.0 equiv), toluene (0.125 M), 110 °C, 16 h, yields of isolated products are

reported (average of two or more runs). [b] $Pd_2(dba)_3$ at 120 °C. [c] 2,5-Bis-arylated **28'** was isolated in 23% yield as an unprecedented T-*shaped* poly(hetero)aromatic structure.

From the chlorinated analogue **2c**, biphenyl-aryltetrazine **21** was obtained in 69% isolated yield only by changing the catalytic system for [$Pd_2(dba)_3$] at 120 °C. In these cross-couplings, boronic acids bearing withdrawing substituents such as CF_3 or F (**22**-**23**) and donating substituents such as *t*-Bu and MeO (**24**-**25**) are tolerated. By using the unequally dihalogenated tetrazines **11a** and **12a**, selective arylation at bromine was successfully achieved with phenyl boronic acids and gave polyaromatic **26** and **27** (59% and 94% isolated yield, respectively) ready for further functionalization at the remaining chloride function. Selective arylation is also possible when bromide and chloride atoms are hold by the same aryl moiety: from **12a'** the tetrazine **28** was obtained in 74% yield (Table 5). The bis-arylated product **28'**, showing a unique T-*shaped* penta-aromatic structure,[20] was also isolated in 23% yield. This result indicates that a first arylation further enhances chlorine reactivity on the same ring. Tetrahalogenated tetrazine **10a** was successfully used to give trichlorinated biphenyl-aryltetrazine **29** in high 97% yield (Table 5). Bis-(biphenyl)-tetrazines **30**-**32**, which were synthesized in excellent yield from dibrominated aryltetrazine **3a** (80 to 90% isolated yield), extend the scope of penta-aromatic structures towards *Z-shaped* compounds, previously unknown as tetrazine analogues of polyphenylenes.[20,21] Compound **31** was characterized by single X-ray diffraction analysis in the solid state (Figure 4). Compared to pristine 3,6-phenyl-1,2,4,5-tetrazine precursor the coplanarity of central aromatic rings is disrupted with torsion angles C7–C2–C1–N2i = 33.7(3) ° (and additionally for biphenyls C9–C8–C7–C2 = 56.5(3) °). This effect is even more pronounced with halogenated aryl groups, as observed in the XRD analysis of compound **10a** (Figure 5) where the

torsion angles are more than doubled with C7–C2–C1–N2i = 69.9(2) ° and C10–C9–C8–N4ii = 75.0(2) ° (see Supporting Information, Figure S7).

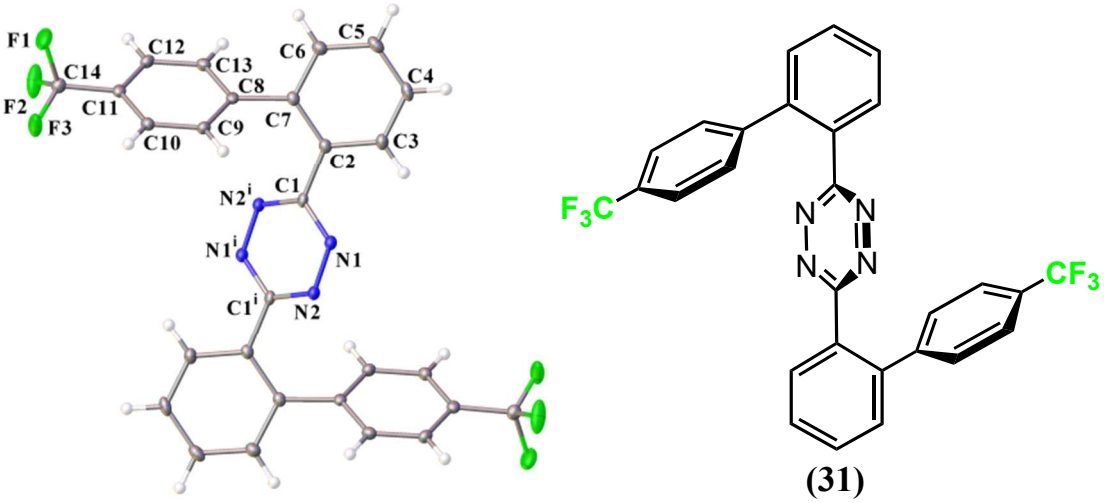


Figure 4. Ortep molecular structure of *Z-shaped* penta-aromatic bis(biphenyl)tetrazine 31 (50% probability ellipsoids. Sym. Op.: (i) 1-x, 1-y, 1-z, see full description in SI, Figure S6).

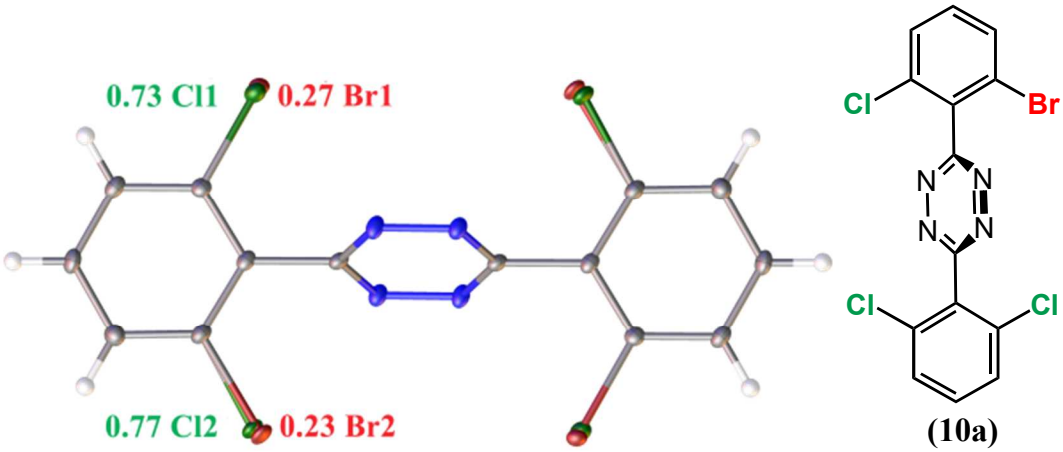
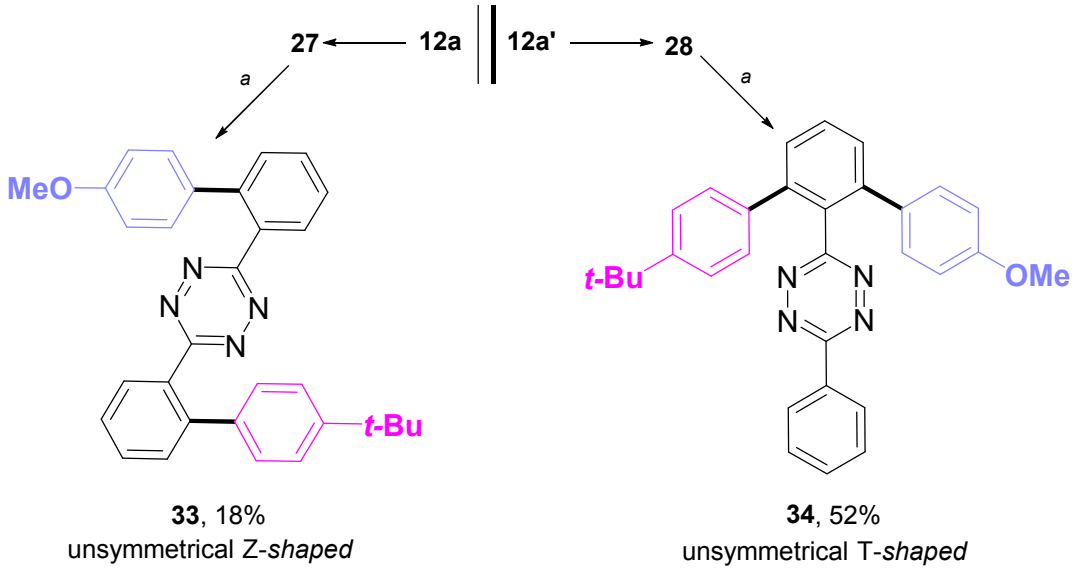


Figure 5. Ortep molecular structure of tetrahalogenated tetrazine 10a (Ortep with 50% probability ellipsoids (Ortep view in Olex2) [Br red, Cl green, N blue, C grey, H white]. Sym. Op.: (i) 1-x, -y, 2-z. The unit cell contains two molecules, only one is shown here. Br and Cl atoms are disordered and occupy the same positions with occupation factors 0.27:0.73 for Br1/Cl1 and 0.23:0.77 for Br2/Cl2, see full description in SI, Figure S7).

We took profit of the halogen-specific Suzuki-Miyaura reaction, which may be tuned with the catalytic system employed, and we used the unequally dihalogenated bromo/chloro **12a** and **12a'** to selectively produce the heteroaromatics **27** and **28** in high yields, respectively (Table 5). We then successfully accessed to unequal bis-(biphenyl) tetrazines with Z-*shaped* and T-*shaped* structures (**33**, **34** in Scheme 5). In the presence of 10 mol% $[Pd_2(dba)_3]$ in mesitylene, 4-methoxyphenylboronic acid successfully coupled with the chlorinated tetrazine **27** to give bis(biphenyl)tetrazine **33** in 18% isolated yield. The same reaction using chlorinated tetrazine **28** (obtained from **12a'**) produces **34** in 52% yield. Notably, those were obtained without palladium auxiliary ligands optimization. This reactivity again evidenced an activation of the chloride function when the supporting aryl group is prefunctionalized.



Scheme 5. Unequally substituted bis-(biphenyl)tetrazines 33 and 34 (conditions: 10 mol% $[Pd_2(dba)_3]$, 2.0 equiv 4-OMe-$C_6H_4B(OH)_2$, 2.0 equiv K_2CO_3, mesitylene 140 °C, 16 h).

CONCLUSION

We have developed a general and efficient palladium catalyzed direct unsymmetrical C–H functionalization of *s*-tetrazines. This method allows the introduction of one to four (un)equivalent halogens in the *ortho*-position of tetrazines in short time reactions each below 1h. As preferential halogenation sequence, the introduction of fluorine and/or chlorine, before bromide, before iodine gives access to *ortho*-functionalized *s*-aryltetrazines bearing two to four different halides. This work provides an efficient and practical entry for further accessing highly unsymmetrical substituted *s*-tetrazine derivatives. We illustrated the potential of C–H activation/halogenation route by synthesizing various new classes of polyaromatic compounds with central tetrazine core; this from using halogen-selective C–C cross-coupling conditions. DFT calculations and XRD analysis have shown that aryl functionalization in biaryl *s*-tetrazines have effect both on the reactivity of the molecules (selectivity in further aryl functionalization), and in the geometry at solid state (polyaromatic planarity rupture). Our current work focused at the investigation of physical and chemical properties of new Z-*shaped* and T-*shaped* tetrazines.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge via the Internet at http://pubs.acs.org." Experimental procedures and spectral data for all new compounds (PDF). Computational details, evaluation of theoretical ratios, reaction paths for isomerization, absolute energies and geometries for all molecules. Crystallographic data (CIF). CCDC 1558814 (**31**), 1558815 (**10a**) contains the supplementary crystallographic data for this paper. These data can be obtained free

of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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AUTHOR INFORMATION

Corresponding Author

*julien.roger@u-bourgogne.fr

*jean-cyrille.hierso@u-bourgogne.fr

ORCID

Clève Dionel MBOYI: 0000-0002-8051-0830

Hélène CATTEY: 0000-0002-4416-7510

Paul FLEURAT-LESSARD: 0000-0003-3114-2522

Julien ROGER: 0000-0002-4964-366X

Jean-Cyrille HIERSO: 0000-0002-2048-647X

Author Contributions

All authors have given approval to the final version of the manuscript.

‡ C. D. M. and C. T. contributed equally to this work.

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Notes

The authors declare no competing financial interest.

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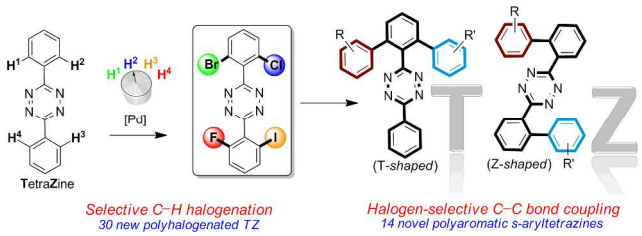

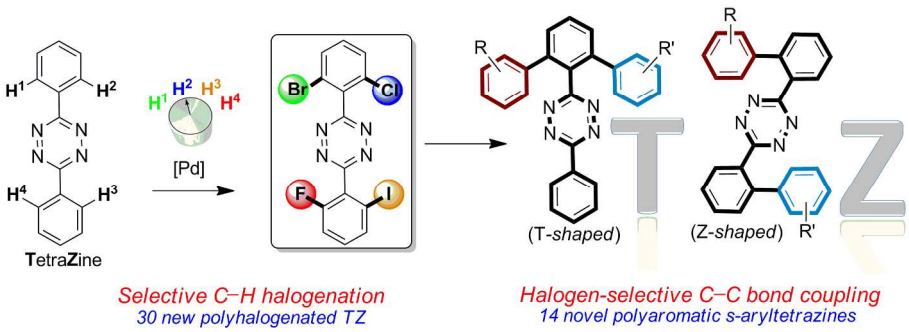

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