C–H Activation

International Edition: DOI: 10.1002/anie.201601082
German Edition: DOI: 10.1002/ange.201601082

Ortho-Functionalized Aryltetrazines by Direct Palladium-Catalyzed C–H Halogenation: Application to Fast Electrophilic Fluorination Reactions

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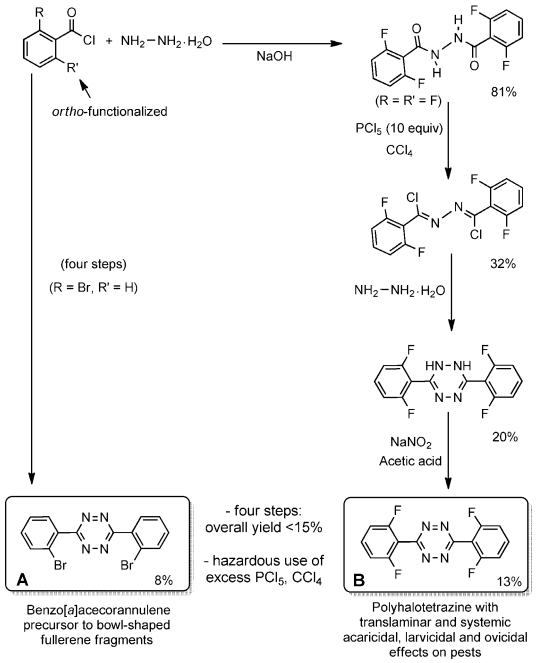
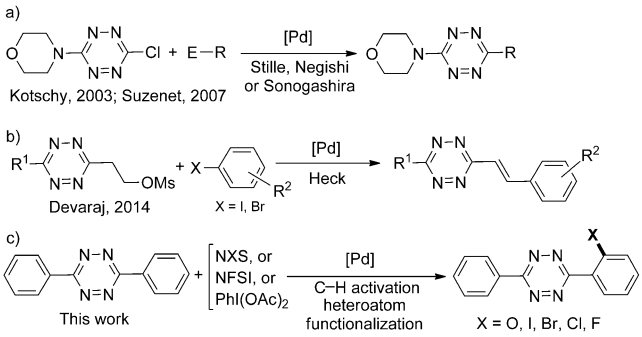
Abstract: *A general catalyzed direct C–H functionalization of s-tetrazines is reported. Under mild reaction conditions, N-directed ortho-C–H activation of tetrazines allows the introduction of various functional groups, thus forming carbon–heteroatom bonds: C–X (X = I, Br, Cl) and C–O. Based on this methodology, we developed electrophilic mono- and poly-ortho-fluorination of tetrazines. Microwave irradiation was optimized to afford fluorinated s-aryltetrazines, with satisfactory selectivity, within only ten minutes. This work provides an efficient and practical entry for further accessing highly substituted tetrazine derivatives (iodo, bromo, chloro, fluoro, and acetate precursors). It gives access to ortho-functionalized aryltetrazines which are difficult to obtain by classical Pinner-like syntheses.*

The chemistry of *s*-tetrazines (1,2,4,5-tetrazines) has attracted increasing interest over the years owing to multiple biochemical, materials, and energy applications resulting from their unique physicochemical properties.[1,2,3] Accordingly, many improvements in tetrazine synthesis have been reported.[4,2a] The aryltetrazine framework is classically derived from the Pinner-like synthesis using hydrazine derivatives with either cyanoaryl or chlorobenzoyle co-reagents. Because of sterics and other factors these syntheses failed to give efficient access to *ortho*-functionalized aryltetrazines. This lack of efficiency is well illustrated with the tedious synthesis of the *ortho*-tetrafluoro tetrazine acaricide **B** which was patented by Chinoin-Sanofi (Scheme 1; for details see Scheme S1 in the Supporting Information).[5] Following a similar multistep methodology, an *ortho*-dibrominated aryltetrazine (**A**), a useful precursor in the synthesis of benzo[*a*]acecorannulene for making bowl-shaped fullerene materials, was obtained in less than 10% yield (Scheme 1).[6] New synthetic access to *ortho*-functionalized tetrazines is clearly desirable. The direct introduction of reactive halo functionality to the *ortho*-position of a preformed tetrazine skeleton, for instance diaryltetrazine, which is commercially available on gram scale, would be a useful synthetic progress.



Scheme 1. General multistep synthesis of *ortho*-functionalized aryltetrazines: Applied to haloaryltetrazines.

Palladium-catalyzed cross-coupling reactions of aromatics for C–C bond formation (Scheme 2a) were recently adapted to the tetrazine series, but with a very limited scope.[1a,7] The



Scheme 2. Palladium-catalyzed tetrazine functionalizations.

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201601082.

tetrazine ring is well-known to act as a ligand for metals, and thus poisons the catalytic activity.[1d] Moreover, tetrazines can be reduced by metals, and subsequent ring opening may occur.[1a,8] Recent work from the group of Devaraj described a practical palladium-catalyzed Heck-type reaction for producing alkenyl tetrazines (Scheme 2b): the combination of appended mesityl group and careful optimization of the reaction conditions allow the palladium chemistry to proceed with excellent functional-group tolerance.[2a]

Ligand-directed C–H bond activation/functionalization by a transition metal has emerged as a powerful method for selectively creating C–C and C–X bonds (X = N, O, S, halogen).[9] We envisioned that nitrogen-directed C–H bond activation/functionalization would be a very attractive approach, thus obviating prefunctionalization of tetrazine substrates. Nitrogen donors in the skeleton are an opportunity to achieve ligand-directed C–H bond functionalization, as long as the reaction conditions remain compatible with the tetrazine nucleus.

We now report a general and direct catalyzed C–H functionalization of tetrazines for the introduction of various useful functional groups, such as halides. Introducing halogen atoms on the aryl ring is a first step towards extending the conjugation of the ring system and the construction of more sophisticated structures through the use of metal-catalyzed coupling reactions. Hence, we report the first efficient C–H functionalization of aryltetrazines. This reaction delivers a straightforward general solution for accessing difficult *ortho*-functionalized aryltetrazines with mono-, di-, tri-, and tetrafunctionalization in a single well-controlled step.

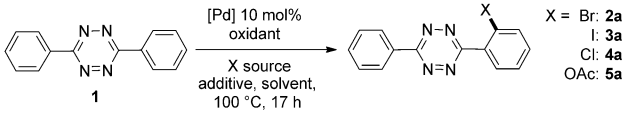
The C–H activation reaction of substituted tetrazines, such as 3,6-diphenyl-1,2,4,5-tetrazine (**1**), is challenging (Table 1) because it can indeed be reduced by metals and then undergo decomposition.[1a] Moreover, the selectivity may be affected by the presence of up to four sp^2C–H bonds at the *ortho* positions of the heteroaromatic ring. We achieved selective monobromination of **1** using *N*-bromosuccinimide (NBS) both as an oxidant and bromination agent, under mild reaction conditions.[10] In the absence of palladium no reaction occurred (entry 1). The reaction of equimolar amounts of **1** and NBS in the presence of 10 mol% of $[Pd(OAc)_2]$ in 1,2-dichloroethane (DCE) at 100 °C for 17 hours led to 75% conversion of **1**, and afforded the expected monobrominated product **2a** along with two dibrominated side-products, **2b** and **2c** (3,6-bis(2-bromophenyl)-1,2,4,5-tetrazine and 3-(2,6-dibromophenyl)-6-phenyl-1,2,4,5-tetrazine, respectively), in a 73:17:10 ratio (entry 2). The compound **2a** can be easily purified and isolated in about 50% yield. Other palladium sources, such as $[PdCl_2]$ and $[Pd(dba)_2]$ led to lower conversions (entries 3 and 4). Increasing the amount of NBS led to higher conversions but was detrimental to the selectivity for **2a** (entries 5 and 6). Improvements were not observed upon replacing NBS with other bromination agents, such as Br_2 or $Br_2CHCHBr_2$ (entries 7 and 8). Improvements were also not observed upon using other solvents (such as CH_3CN; entry 9), ligands, and additives (see Table S1).

Highly selective functionalization of **1** with a variety of valuable functional groups was achieved by tuning our protocol as follows. Iodination of **1** was achieved using *N*-iodosuccinimide (NIS) in the presence of 10 mol% $[Pd(dba)_2]$ in DCE to afford 55% conversion and a 89:11 ratio of the monoiodinated product **3a** to the symmetrical diiodinated analogue **3b** ((3,6-bis(2-iodophenyl)-1,2,4,5-tetrazine; Table 1, entry 10). Chlorination of **1** was achieved using *N*-chlorosuccinimide (NCS) and 10 mol% $[PdCl_2]$ in HOAc at 120 °C (entry 11) to afford the monochlorinated tetrazine **4a** with 92% selectivity (see Tables S3 and S5). The scope of such an unprecedented C–H functionalization of *s*-tetrazine was extended to acetoxylation reactions using $PhI(OAc)_2$ and 10 mol% $[Pd(OAc)_2]$ in HOAc to afford pure **5a** in 51% yield (entry 12).

To demonstrate the power of direct C–H halogenation of aryltetrazine we optimized the synthesis of **A** (Scheme 1) to involve a single step from the commercially available **1** by using 3 equivalents of NBS. **A** was isolated in 47% yield after work-up while the monobrominated species **2a** (25%) was recovered for additional selective bromination.

The four C–H functionalizations of *s*-tetrazine were also examined. Tetrahalogenation of *s*-tetrazine was achieved upon adjusting the amount of the halogenation reagent (Table 2). By using 8 equivalents of NBS and 10 mol% of a palladium catalyst, full conversion of **1** was achieved and afforded the tetrabrominated tetrazine **2e** in 98% yield upon isolation (entry 1). The reaction was even faster when using a smaller amount of NBS (entry 2) in the presence of 10 mol% of $[Pd(OAc)_2]$ in HOAc at 120 °C. When using the same catalytic system, multiple C–H halogenation reactions were successfully achieved with other *N*-halosuccinimides (10 equiv) albeit in lower yields (entries 3 and 4): the tetraiodotetrazine **3e** and tetrachlorotetrazine **4e** were obtained from NIS (71% yield) and NCS (80% yield), respectively. Patents and reports have highlighted the acar-

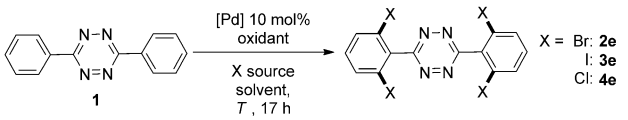
Table 1: C–H monofunctionalization of 3,6-diphenyl-1,2,4,5-tetrazine (**1**).[a]



Entry	[Pd]	Oxidant (equiv)	Solvent	Conv. [%]	Yield [%]
1	–	NBS (1.0)	DCE	0	0
2	$Pd(OAc)_2$	NBS (1.0)	DCE	75	**2a**: 55 (48)
3	$PdCl_2$	NBS (1.0)	DCE	26	**2a**: 26
4	$[Pd(dba)_2]$	NBS (1.0)	DCE	67	**2a**: 54 (45)
5	$[Pd(dba)_2]$	NBS (1.7)	DCE	87	**2a**: 57
6	$[Pd(dba)_2]$	NBS (2.2)	DCE	96	**2a**: 41
7	$[Pd(dba)_2]$	Br_2 (2.2)	DCE	0	0
8	$[Pd(dba)_2]$	$(Br_2CH)_2$ (2.2)	DCE	0	0
9	$[Pd(dba)_2]$	NBS (1.7)	CH_3CN	0	0
10	$[Pd(dba)_2]$	NIS (1.0)	DCE	55	**3a**: 49 (33)
11[b]	$PdCl_2$	NCS (1.0)	HOAc	48	**4a**: 44 (32)
12	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.0)	HOAc	84	**5a**: 64 (51)

[a] Reaction conditions: **1** (1 equiv), [Pd] (10 mol%), X source (1.0 to 2.2 equiv), solvent (0.125 M), 100 °C, under argon, 17 h. Yield determined by ^{1}H NMR spectroscopy. Yield of isolated product given within parentheses. [b] 120 °C. dba = dibenzylideneacetone, DCE = 1,2-dichloroethane.

Table 2: Tetrafunctionalization of **1**.[a]



1

Entry	[Pd]	Oxidant (equiv)	Solvent	*T* [°C]	Yield [%]
1	$[Pd(dba)_2]$	NBS (8.0)	HOAc	100	**2e**: 99 (98)
2	$Pd(OAc)_2$	NBS (6.0)	HOAc	120	**2e**: 99 (89)
3	$Pd(OAc)_2$	NIS (12.0)	HOAc	120	**3e**: 71 (64)
4	$Pd(OAc)_2$	NCS (10.0)	HOAc	120	**4e**: 80 (34)

[a] Reaction conditions: **1** (1 equiv), [Pd] (10 mol%), NXS (6 to 12 equiv), solvent (0.125 M), under argon, 17 h. Yield determined by ^{1}H NMR spectroscopy. Yield of isolated product given within parentheses.

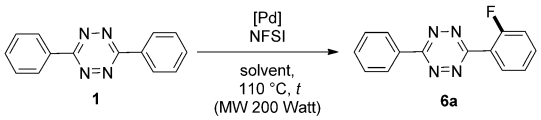
icidal potential of halogenated aryltetrazine of the Clofentezine family [3,6-bis-(2-chlorophenyl)-1,2,4,5-tetrazine (**4b**); see the Supporting Information], which overcomes the resistance developed by pests to classical organophosphorous pesticides.[11] By using our method, Clofentezine was synthesized and isolated in 35% yield in a single step by using 5 equivalents of NCS with **1**, thus providing a valuable alternative to traditional multistep pathways employed.

Based on these results we also examined direct C–H fluorination reactions. We were especially eager to test tetrafluorination of **1** to provide the acaracide **B** (Scheme 1), which was isolated in 13% yield from a multistep synthesis involving large amounts of hazardous PCl_5 and hepatotoxin CCl_4.[5] In addition, with regard to catalyzed fluorination reactions, a fast conversion time is an important parameter for potential radiolabeling involving the radiative isotope ^{18}F, which has a short half-life ($t_{1/2} = 110$ min).[12] Examples of C–H bond activation using N-containing directing groups have been reported, and generally involves a single directing group.[13,14] We have here the opportunity for easy polyfluorination, which is potentially useful for obtaining higher radiochemical yields.

The reaction between **1** and 1 equivalent of *N*-fluorobenzenesulfonimide (NFSI) was conducted in nitromethane at 110 °C, using 10 mol% of $[Pd(dba)_2]$. The monofluorinated compound **6a** was isolated in 30% yield, with a corresponding conversion of **1** at around 41% over 17 hours (Table 3, lines 1–7). The reaction time was reduced to 30 minutes upon using microwave irradiation (entries 8–11), 20 mol% of $[Pd(dba)_2]$, and trifluoromethylbenzene ($PhCF_3$) as a solvent at 110 °C in the presence of air (entry 8). The amount of NFSI was crucial to achieve full conversion of **1**. By using 2.5 equivalents of NFSI, **1** was fully converted into the mono- and difluorinated species **6a**, **6b**, and **6c** (3-(2,6-difluorophenyl)-6-phenyl-1,2,4,5-tetrazine) in a 63:27:9 ratio (entry 11). A 77:18:5 ratio with a 91% conversion of **1** and 50% yield of the isolated **6a** was achieved by using 2.2 equivalents of NFSI (entry 10).

Then, the synthesis of **B** was achieved starting from either **1** or its difluorinated derivative **6b** (Scheme 3). The one step synthesis of **B** from **1** and **6b** was achieved in 74 and 87% conversions, respectively, and in 36 and 46% yield, respectively, upon isolation. The lower yield of the isolated product is a result of stability issues during chromatography on silica.

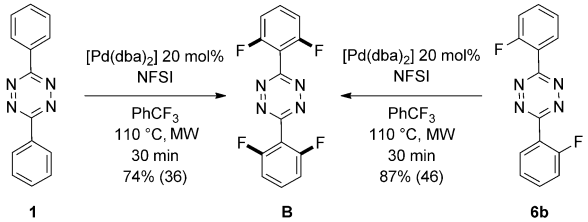
Table 3: Fluorination of **1**: Optimization for fast reaction time and good selectivity in monofluorinated product.[a]



1 **6a**

Entry	[Pd]	NFSI (equiv)	Solvent	*T*	Yield [%]
1	$PdCl_2$	1.0	CH_3NO_2	17 h	34[b]
2	$[\{PdCl(allyl)\}_2]$	1.0	CH_3NO_2	17 h	45[b]
3	$[Pd(dba)_2]$	1.0	CH_3NO_2	17 h	41 (30)
4	$[Pd_2(dba)_3]$	1.0	CH_3NO_2	17 h	35
5[c]	$[Pd_2(dba)_3]$	1.0	CH_3NO_2	17 h	46
6	$[Pd_2(dba)_3]$	1.5	CH_3NO_2	17 h	57
7	$[Pd_2(dba)_3]$	1.0	$PhCF_3$	17 h	47
8[d]	$[Pd(dba)_2]$	1.5	$PhCF_3$	30 min	62
9[d]	$[Pd(dba)_2]$	2.0	$PhCF_3$	10 min	71 (44)
10[d]	$[Pd(dba)_2]$	2.2	$PhCF_3$	10 min	70 (50)
11[d]	$[Pd(dba)_2]$	2.5	$PhCF_3$	10 min	63 (47)

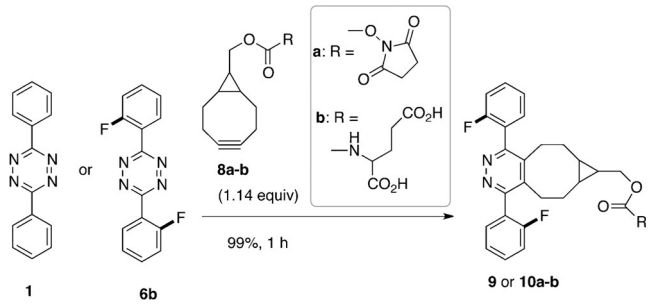
[a] Reaction conditions: 3,6-diphenyl-1,2,4,5-tetrazine **1** (1 equiv), [Pd] (10 mol%), NFSI (1–2.5 equiv), solvent (0.125 M), 110 °C, under argon. Yield determined by ^{1}H and ^{19}F NMR spectroscopy. Yield of isolated product given within parentheses. [b] Chlorination product was detected. [c] $[Pd_2(dba)_3]$ (20 mol%). [d] $[Pd(dba)_2]$ (20 mol%), microwave (MW) 200 W, under air.



1 **B** **6b**

Scheme 3. Tetrafluorination of 3,6-diphenyl-1,2,4,5-tetrazine (**1**) and 3,6-bis(2-fluorophenyl)-1,2,4,5-tetrazine (**6b**). NFSI (8–12 equiv) was used.

To further demonstrate the interest of such a straightforward method to obtain fluorinated tetrazines, we tested their ability to undergo cycloaddition reaction with pristine **1**. Electron-deficient diene tetrazines can react with electron-rich dienophiles to form a Diels–Alder adduct (inverse electron-demand Diels–Alder reaction; iEDDA), which is then converted into a pyridazine upon extrusion of N_2. Because of its fast reactivity and bioorthogonal nature, this reaction has already been utilized for bioconjugation in vitro and in vivo, and has also been applied successfully in polymer and materials science.[15] We tested the iEDDA reaction with the starting materials **1** and **6b**. The bicyclononyne **8a**, used (Scheme 4) for iEDDA reactions, contains a terminal dioxopyrroldinyl ester which allows easy modification with many biochemical products from peptide coupling.[16] Strain-promoted [4+2] cycloaddition of 1,2,4,5-tetrazines (**1** or **6b**) with **8a** was monitored by UV/Vis spectroscopy with examination of the decay of the absorption band at $\lambda = 540$ nm for **6b** (to give **9**) and $\lambda = 550$ nm for **1** (see Figure S1). The reaction



Scheme 4. Cycloadditions of **1** and **6b**.

went to completion in less than 1 hour with **6b**, and a slightly longer reaction time was needed for **1**. Such a result shows that although the presence of the fluorine atoms did not preclude cycloaddition, they favorably influence the electron density of the dieneophile and thus increase the rate of the reaction (for kinetic curves see Figure S3: rate for **6b** cycloaddition $k_{app} = 0.0755\ min^{-1}$ vs. $0.0355\ min^{-1}$ for **1**). As a definitive proof-of-concept illustrating a bioconjugation scenario, **8a** was conjugated with L-glutamic acid to afford **8b**, which was subsequently efficiently reacted with **6b** to afford the pyridazine **10b**. Further work is ongoing regarding the radiofluorination transfer.[17]

In summary, we reported the *ortho*-C–H activation of *s*-tetrazines, a reaction which allows the introduction of various functional groups to the tetrazine core. A new and efficient methodology was developed for electrophilic *ortho*-fluorination of tetrazines, using NFSI and microwave irradiation, in only ten minutes when open to air. Hence, this work provides an efficient and practical entry to access highly substituted tetrazine derivatives, and will facilitate the development of *ortho*-functionalized aryltetrazines as useful precursors to materials and bioactive compounds which are difficult to obtain by using the typical Pinner-like syntheses.

Acknowledgments

This work was supported by the Université de Bourgogne (MESR PhD grant for CT), the Région Bourgogne (PARI II CDEA program), and the CNRS (3MIM-P4 program). We thank ChemaTech® for generous gift of bicyclononyne. We are thankful for specific support from the Institut Universitaire de France IUF (JCH) and CNRS (RD).

Keywords: C–H activation · fluorine · halogenation · heterocycles · palladium

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 5555–5559
Angew. Chem. **2016**, *128*, 5645–5649

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Received: January 30, 2016
Revised: February 23, 2016
Published online: March 24, 2016

