COMMUNICATIONS doi.org/10.1002/adsc.202300875 Advanced Synthesis & Catalysis

Palladium-Catalyzed Domino Reaction for the Synthesis of 3-Amino 1,2,4-Benzothiadiazine 1,1-Dioxides

Renè Hommelsheim,[a] Robin van Nahl,[+a] Lena M. Hanek,[+a] Jas S. Ward,[b] Kari Rissanen,[b] and Carsten Bolm[a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52074 Aachen, Germany
E-mail: carsten.bolm@oc.rwth-aachen.de
[b] University of Jyvaskyla, Department of Chemistry, Jyväskylä 40014, Finland

[+] These authors contributed equally.

Manuscript received: August 10, 2023; Revised manuscript received: October 13, 2023;
Version of record online: ■■, ■■

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202300875

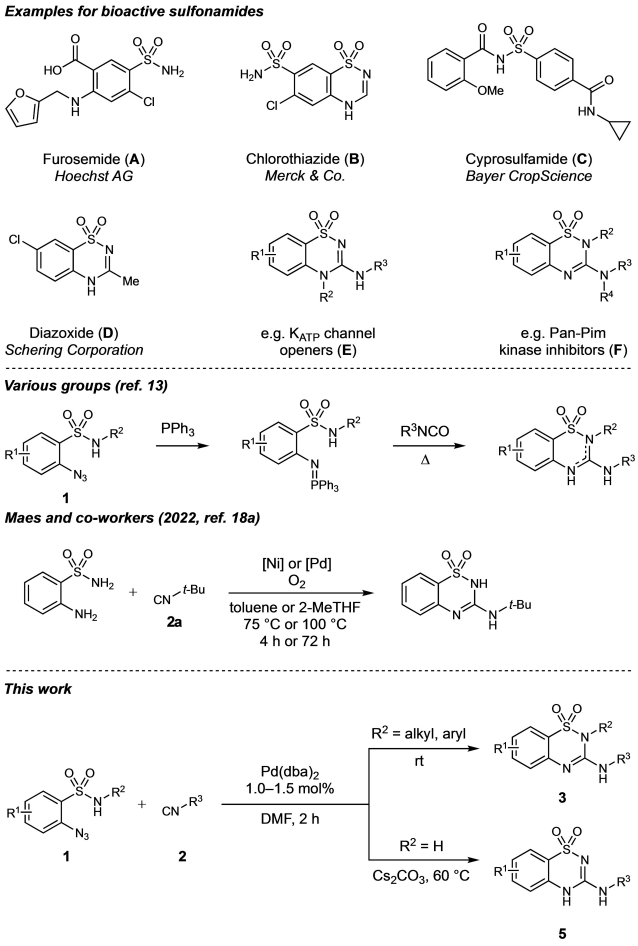
Abstract: A palladium-catalyzed domino reaction of 2-azidosulfonamides and isocyanides enables the synthesis of 3-amino-substituted 1,2,4-benzothiadiazine 1,1-dioxides at room temperature. By applying commercially available $Pd(dba)_2$ in catalyst loadings as low as 1.0 mol%, a variety of 21 differently substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides can be prepared within 2 h. Moreover, the developed protocol gives access to the related 4*H* heterocycles.

Keywords: Domino reactions; palladium catalysis; sulfur heterocycles; sulfonamides; azides

Sulfonamides are ubiquitous in medicinal chemistry. Due to their versatile biological activities, they are widely applied as high-selling drugs with anti-microbial, anti-diabetic, anti-hypertensive, or anti-inflammatory properties.[1] Two of the most popular sulfonamides are Furosemide (**A**)[2] and Chlorothiazide (**B**) (Scheme 1),[3] which belong to the essential medicines according to the World Health Organization (WHO).[4] While Furosemide (**A**) is a loop diuretic,[2] Chlorothiazide (**B**) is an antihypertensive and diuretic.[3] Besides their applications in medicinal chemistry, sulfonamides are also broadly utilized in crop protection,[5] as exemplified by Cyprosulfamide (**C**).[5a,6]

Among bioactive sulfonamides, the corresponding heterocycles named sultams have attracted particular interest in the development of new active pharmaceutical ingredients.[7] Examples include 1,2,4-benzothiadiazine 1,1-dioxides Chlorothiazide (**B**) or Diazoxide (**D**),[8] which both revealed various pharmacological activities.[9] Along the same lines, their related 3-amino-substituted derivatives **E**[10] and **F**[11] have been intensively studied (Scheme 1). In addition, chiral derivatives of **E** found use as asymmetric organocatalysts.[12]

For the synthesis of 3-amino-substituted 1,2,4-benzothiadiazine 1,1-dioxides, either a two-step approach involving an Aza-Wittig-type reaction of 2-azidosulfonamides (**1**) and isocyanates[13] or multiple-step syntheses from various starting materials have been established over the past decades (Scheme 1).[10a–k,11,14] In the case of the Aza-Wittig-type reactions,[15] 2-azidosulfonamides (**1**) react with phosphines (usually triphenylphosphine) to give the corresponding iminophosphoranes. The latter then react with isocyanates forming carbodiimide intermediates which subsequently yield the desired heterocycles. Although the overall yields of this approach are moderate to excellent, the protocols commonly suffer from harsh reaction conditions and long reaction times.[13] Another strategy is based on condensations of *o*-aminoarylsulfonamides or *o*-halogenated arylsulfonyl-halides with suitable dielectrophiles or dinucleophiles. Although this approach enables a one-step synthesis of the desired heterocycles, the yields have remained low to moderate and harsh reaction conditions are required in most of the protocols.[10l–n,16] Finally, Maes and co-workers demonstrated in a single



Scheme 1. Examples for biologically relevant sulfonamides and synthetic approaches for the preparation of sultams.

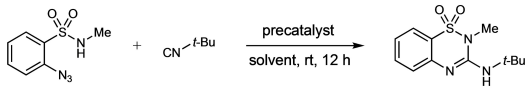
example that 3-amino-substituted 1,2,4-benzothiadiazine 1,1-dioxides can be prepared by metal-catalyzed oxidative imidoylation reactions of 2-aminoarylsulfonamides with isocyanides.[17,18] Using a nickel or a palladium catalyst the product was obtained in yields of 79% and 69%, respectively (Scheme 1).

As part of our ongoing research on the synthesis of sulfur-containing heterocycles,[19] we recently reported a highly efficient protocol for the synthesis of 3-amino-substituted benzothiadiazine oxides.[19a] When applying tetrakis(triphenylphosphine) palladium(0) in catalyst loadings of 0.25–1.5 mol%, 2-azidosulfoximines reacted with isocyanides to the corresponding heterocycles under ambient conditions and in short reaction times. Motivated by these results and in light of previous studies on palladium-catalyzed domino reactions of isocyanides and azides,[20] we wondered if a similar approach could be applied for accessing 3-amino-substituted 1,2,4-benzothiadiazine 1,1-dioxides. Herein, we demonstrate the success of this approach (Scheme 1).

The investigations were started by applying the previously developed protocol[19a,20] in the model reaction of 2-azidobenzenesulfonamide **1a** with isocyanide **2a** and tetrakis(triphenylphosphine)-palladium(0) as a metal pre-catalyst (Table 1, entry 1). To our delight, our initial hypothesis was correct, and compound **3aa** was isolated in 29% yield. Next, various metal pre-catalysts (Table 1, entry 1–7) were screened. The application of palladium(II)-acetate, rhodium(II)-acetate and pentamethylcyclopentadienylrhodium(III)dichloride dimer (Table 1, entry 2–4) gave compound **3aa** only in poor to moderate yields (8%, 13%, and 44% yield, respectively). However, the application of the commercially available and moderately air stable palladium(0) pre-catalysts tris(dibenzylideneacetone)-dipalladium(0) [$Pd_2(dba)_3$] and bis(dibenzylidene-aceton)palladium(0) [Pd-$(dba)_2$][21] improved the yield significantly and heterocycle **3aa** was isolated in 93% and 98% yield, respectively. Maintaining $Pd(dba)_2$ as the metal pre-catalyst, the catalyst loading was investigated next. While decreasing the catalyst loading from 5 mol% to 1.5 mol% had no influence on the reaction providing **3aa** in 98% yield (Table 1, entry 8), a further reduction to 1.0 mol% or 0.5 mol% led to a decreased yield of 94% or 43%, respectively (Table 1, entry 9 and 10). Next, various polar and non-polar aprotic solvents were screened (Table 1, entry 8, 11–14). Among the tested solvents DMF, THF, DCM, MeCN, and toluene, DMF proved optimal. In the last step, the reaction time was reduced to 2 h (Table 1, entry 15), providing heterocycle **3aa** in 95% yield. When performing the reaction in the absence of a metal catalyst (Table 1, entry 16), no product formation was observed, confirming the importance of a catalytic process.[22]

Next, the substrate scope was investigated to evaluate the applicability of the developed protocol (Scheme 2). By applying the optimal reaction conditions (Table 1, entry 15), various aliphatic (**2a–2i**) and aromatic isocyanides (**2j–2r**) were tested in the reaction with model azide **1a** first. Comparing the results for compounds **3aa** (95%), **3ab** (99%), **3ac** (96%), **3ad** (98%), and **3ae** (96%), resulting from the reaction of **1a** with alkyl-substituted isocyanides **2a–e**, respectively, revealed that the degree of substitution had only a minor effect. As expected, heterocycle **3ad**, resulting from the reaction of model azide **1a** with isocyanide ***S*-2d**, was observed under full retention of stereochemistry.[23] The reaction of **1a** with isocyanide **2f** bearing a morpholino group proceeded well, and the corresponding product **3af** was isolated in 96% yield. While the electron-rich benzyl isocyanide **2g** was well tolerated and the corresponding product **3ag** was observed in 93% yield [using 2.5 mol% $Pd(dba_2)$], electron-poor isocyanides **2h**[24] and **2i** proved to be incompatible, and only trace amounts of compound **3ah** were detected by HRMS.

Table 1. Optimization of the reaction conditions.



1a **2a** **3aa**

Entry[a]	Pre-catalyst	mol%	Solvent	Yield [%][b]
1	$Pd(PPh_3)_4$	5.0	DMF	29
2	$Pd(OAc)_2$	5.0	DMF	8
3	$Rh_2(OAc)_4$	5.0	DMF	13
4	$[Cp^*RhCl_2]_2$	5.0	DMF	44
5	$Co(acac)_3$	5.0	DMF	0
6	$Pd_2(dba)_3$	5.0	DMF	93
7	$Pd(dba)_2$	5.0	DMF	96
8	$Pd(dba)_2$	1.5	DMF	98
9	$Pd(dba)_2$	1.0	DMF	94
10	$Pd(dba)_2$	0.5	DMF	43
11	$Pd(dba)_2$	1.5	THF	86
12	$Pd(dba)_2$	1.5	DCM	61
13	$Pd(dba)_2$	1.5	MeCN	23
14	$Pd(dba)_2$	1.5	toluene	91
15[c]	**$Pd(dba)_2$**	**1.5**	**DMF**	**95**
16	–	–	DMF	0

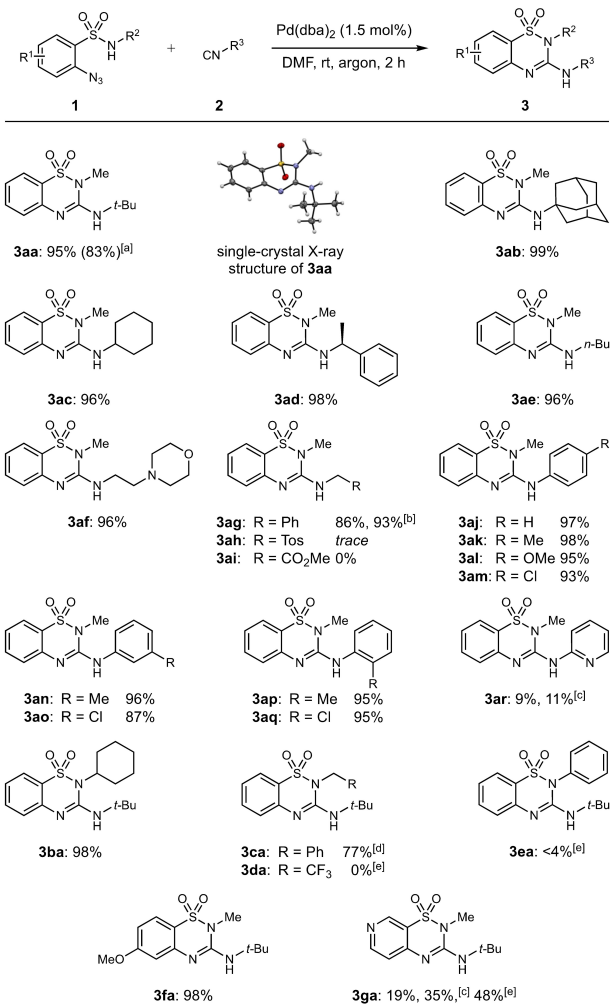
[a] Reaction conditions: Metal pre-catalyst, **1a** (0.4 mmol), **2a** (0.44 mmol), solvent (2.0 mL), argon atmosphere, rt, 12 h.
[b] Yields determined after column chromatography.
[c] Reaction time: 2 h.

The broad substrate tolerance was further confirmed by successfully applying various aromatic isocyanides (**2j**–**2r**) in the reaction with model azide **1a** (Scheme 2). The comparison of the results for electron-donating and electron-withdrawing isocyanides **2l** and **2m**, respectively, indicates that electronic effects have no influence on the yield of the reaction. While no stereoelectronic effect was observed in the series of *o*- (**2p**), *m*- (**2n**) and *p*-tolyl (**2k**) substituted isocyanides, giving the corresponding products **3ap** (95%), **3an** (96%) and **3k** (98%) in generally excellent yields, a minor effect was observed in the series of the corresponding chlorophenyl substituted heterocycles [**3aq** (95%), **3ao** (87%) and **3am** (93%)]. The reaction of **1a** with pyridyl-substituted isocyanide **2r** proceeded poorly, and the corresponding product **3ar** was isolated in only 9% yield. The application of higher catalyst loadings (5.0 mol%) in this reaction had no positive influence on the yield. The proposed molecular structure for compound **3aa** was confirmed by single-crystal X-ray analysis.[25]

In the next step, a range of 2-azidosulfonamides **1** were tested in the reaction with model isocyanide **2a** (Scheme 2). Applying the optimal reaction conditions, *N*-cyclohexyl substituted sulfonamide **1b** was well tolerated, and heterocycle **3ba** was isolated in 98% yield. The reaction of *N*-benzyl-substituted sulfonamide (**1c**) required a higher catalyst loading (7.5 mol%), providing the corresponding product in 77% yield. No product formation was observed when *N*-trifluoroethyl-substituted sulfonamide **1d** was used, even when 10 mol% of the pre-catalyst was applied. *N*-Phenyl-substituted sulfonamide **1e** reacted poorly under those conditions, too. As a consequence, the results for compounds **3ba**–**3ea** show that the electronic properties of the *N*-bonded substituent have a crucial influence on the reaction outcome. The application of aryl-substituted sulfonamide **1f** in the reaction with isocyanide **2a** provided compound **3fa** in 98% yield. Pyridyl-substituted sulfonamide **1g** reacted poorly, and compound **3ga** was isolated in only 19% yield under the optimal reaction conditions [1.5 mol% $Pd(dba)_2$]. However, the yield could be improved up to 48% by applying higher catalyst loadings [10.0 mol% $Pd(dba)_2$].[26]

To test the scalability of the developed protocol, a gram-scale experiment using 5.0 mmol of compound **1a** was conducted. To our delight, heterocycle **3aa** was isolated in 83% yield, thus demonstrating a good scalability of the developed protocol.

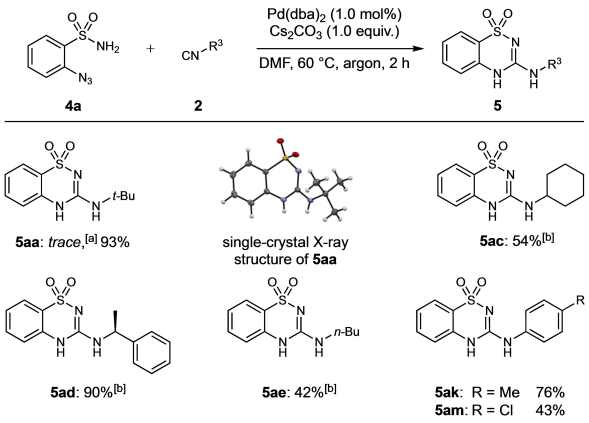
To further elaborate on the potential of the palladium-catalyzed reaction of 2-azidosulfonamides with isocyanides, the synthesis of related 4*H*-1,2,4-benzothiadiazine 1,1-dioxides **5** was targeted next (Scheme 3). Initially, the reaction conditions that had been previously found to be optimal for the synthesis of compound **3aa** (Table 1, entry 15) were applied to the reaction of 2-azidobenzene-sulfonamide (**4a**) and



Scheme 2. Evaluation of the substrate scope with respect to isocyanides **2** and azides **1**. Reaction conditions: **1** (0.4 mmol), **2** (0.44 mmol), $Pd(dba)_2$ (0.006 mmol, 1.5 mol%), DMF (2.0 mL), rt, 2 h.[a] Gram-scale experiment using 5.0 mmol of **1a**.[b–e] Use of 2.5 mol%, 5.0 mol%, 7.5 mol%, and 10 mol% of the pre-catalyst, respectively.

isocyanide **2a**. However, only trace amounts of the desired product **5aa** were observed. After a comprehensive adjustment of the reaction conditions, including the catalyst loading, equivalents, temperature, concentration and the addition of alkali bases as an additive,[22] compound **5aa** was isolated in 93% yield. In particular, the addition of Cs_2CO_3 was essential to allow higher turnover numbers and consequently lower catalyst loadings.[27,28]

With the adjusted optimal reaction conditions in hand, the substrate tolerance with respect to various isocyanides **2** was studied. The reactions of tertiary (**2a**), secondary (**2c** and **2d**) and primary (**2e**) aliphatic isocyanides with azide **4a** proceeded well and the respective heterocycles (**5aa**–**5ae**) were isolated in moderate to excellent yields. In this series, higher

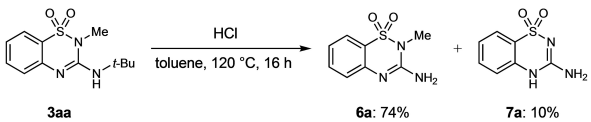


Scheme 3. Evaluation of the substrate scope for the synthesis of heterocycle **5**. Reaction conditions: **4a** (0.4 mmol), **2** (0.6 mmol), Cs_2CO_3 (1.0 equiv.), $Pd(dba)_2$ (0.004 mmol, 1.0 mol%), DMF (2.0 mL), 60 °C, 2 h.[a] Applying the previous optimal reaction conditions (Table 1, entry 15).[b] Use of 5.0 mol% of $Pd(dba)_2$.

catalyst loadings of 5.0 mol% of $Pd(dba)_2$ were necessary for substrate **5ac**, **5ad** and **5ae**. To evaluate the potential of the developed methodology in the synthesis of potential chiral hydrogen-bond donor catalyst,[12] the reaction of model azide **4a** with isocyanide ***S*-2d** was investigated. To our delight, the reaction procced smoothly and compound **5ad** was isolated in 90% yield and under full retention of stereochemistry.[23] Moreover, aromatic isocyanides **2k** and **2m** were tolerated, providing the corresponding products in 76% (for **5ak**) and 43% (for **5am**) yields, respectively. X-ray crystallographic analysis provided proof for the proposed molecular structure for heterocycle **5aa**.[25]

Next, compound **3aa** was used to investigate and demonstrate a dealkylation strategy leading to free amine **6a** as potential 1,2,4-benzothiadiazine 1,1-dioxide building block. By applying literature-known conditions, compound **3aa** was treated with HCl to test the viability of the envisaged dealkylation path (Scheme 4).[18,19a] To our delight, the desired free amine **6a** could be obtained in 74% yield. As by-product, however, demethylated product **7a** was formed in 10% yield.

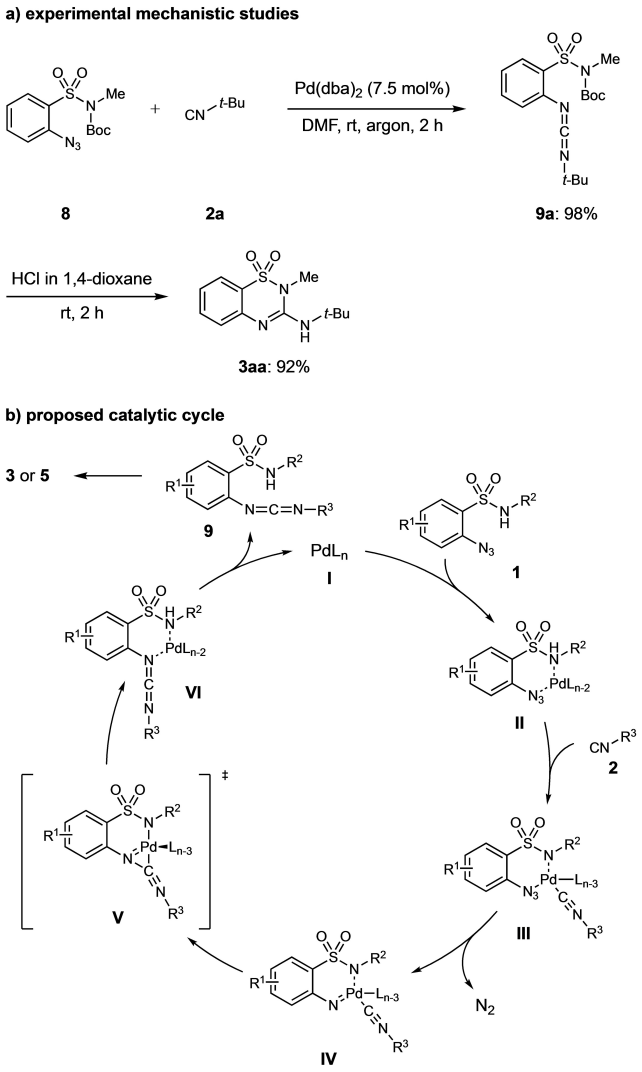
Finally, we decided to investigate the reaction mechanism. Based on previous studies[19a,20b] we



Scheme 4. Dealkylation strategy for compound **3aa**, enabling the synthesis of free amine **6a**.

propose a domino reaction sequence involving the formation of a carbodiimide as a potential key intermediate. To test this hypothesis, the reaction of Boc-protected 2-azido sulfonamide **8** with model isocyanide **2a** was investigated (Scheme 5).[19a]

Applying modified optimal reaction conditions [7.5 mol% $Pd(dba_2)$] Boc-protected carbodiimide **9a** was isolated in 98% yield. Subsequent treatment of **9a** with hydrochloric acid gave the corresponding heterocycle **3aa** in 92% yield in the absence of metal-catalyst, indicating that the reaction proceeds by formation of a carbodiimide as a potential intermediate. Based on these findings and previous reports,[19a,20b] we propose a catalytic cycle depicted in Scheme 5. The reaction sequence is initiated by coordination of 2-azidosulfonamide **1** to the active metal catalyst **I** to form metal complex **II**. Through coordination of isocyanide **2** complex **III** is formed, which after elimination of N_2 forms palladium-imido complex **IV**.[20b] In the next step, complex **IV** undergoes nitrene transfer to form complex **VI** over transition state **V**. Upon decordination, the active metal catalyst **I** is regenerated and carbodiimide **9** is formed. The latter then can undergo an intramolecular cyclization by a nucleophilic 6-*exo*-*dig* attack to yield the desired heterocycle **3** or **5**.[20b,29]



Scheme 5. Reaction mechanism of the palladium-catalyzed domino reaction: a) mechanistic investigations; b) proposed catalytic cycle.

In conclusion, we developed a palladium-catalyzed domino reaction for the synthesis of 1,2,4-benzothiadiazine 1,1-dioxides by starting from 2-azidosulfonamides **1**[30] and isocyanides **2**. With $Pd(dba)_2$ as a commercially available pre-catalyst used in low loadings (in most of the examples 1.5 mol%), a variety of 21 3-amino-2*H*-1,2,4-benzothiadiazine 1,1-dioxides **3** were synthesized in high yields tolerating aliphatic-, aromatic- and heterocyclic substituted isocyanides. Moreover, the protocol enables the preparation of the related 4*H*-1,2,4-benzothiadiazine 1,1-dioxides **5** in moderate to excellent yields (42–93%). We could further demonstrate the dealkylation of heterocycle **3**, which allowed access to the corresponding free amine **6** as a potential synthetic building block. Furthermore, experimental mechanistic studies indicated that a domino reaction sequence involving a carbodiimide intermediate is taking place.

Experimental Section

All experimental details, including experimental procedures, characterization data for new compounds, X-ray crystallographic data, solvent- and temperature-dependent NMR studies, and NMR spectra for new compounds, can be found in the Supporting Information.

Experimental Procedure for Synthesizing N-substituted 3-Amino 1,2,4-Benzothiadiazine 1,1-dioxides 3

The procedure is analogous to the one developed for the synthesis of 3-amino-substituted benzothiadiazine oxides.[19a] Bis(dibenzylideneacetone)palladium(0) (3.5 mg, 0.006 mmol, 1.5 mol%) and the corresponding 2-azido-benzenesulfonamide (**1**, 0.4 mmol, 1.0 equiv.) were charged under air atmosphere in an oven dried Schlenk tube. The tube was evacuated and backfilled with argon three times. DMF (2.0 mL) and the corresponding isocyanides (**2**, 0.44 mmol, 1.1 equiv.) were added, and the resulting solution was stirred for 2 h at room temperature. Then, EtOAc (ca. 60 mL) was added and the organic phase was washed with brine (3×ca. 40 mL). The organic phase was dried over $MgSO_4$, SiO_2 was added and the volatiles were removed under vacuum. Purification by column chromatography (column diameter: ca. 2 cm, column length: ca. 35 cm) on silica using *n*-pentane: EtOAc as gradient solution (5:1 → 3:1) afforded the targeted 3-amino 1,2,4-benzothiadiazine 1,1-dioxide **3**.

Experimental Procedure for Synthesizing N-unsubstituted 3-Amino Benzothiadiazine 1,1-dioxides 5

The procedure is analogous to the one developed for the synthesis of 3-amino-substituted benzothiadiazine oxides.[19a] Bis(dibenzylideneacetone)palladium(0) (2.3 mg, 0.004 mmol, 1.0 mol%), Cs_2CO_3 (131 mg, 0.4 mmol, 1.0 equiv.), and 2-azidobenzenesulfonamide (**4a**, 79.3 mg, 0.4 mmol, 1.0 equiv.) were charged under air atmosphere in an oven dried Schlenk tube. The tube was evacuated and backfilled with argon three times. DMF (2.0 mL) and the corresponding isocyanides (**2**, 0.6 mmol, 1.5 equiv.) were added and the resulting suspension was stirred at 500 rpm for 2 h at 60 °C in a pre-heated aluminum block. Then, EtOAc (ca. 60 mL) was added, and the organic phase was washed with brine (3×ca. 40 mL). The organic phase was dried over $MgSO_4$, SiO_2 was added and the volatiles were removed under vacuum. Purification by column chromatography (column diameter: ca. 2 cm, column length: ca. 35 cm) on silica using *n*-pentane: EtOAc: MeOH as gradient solution (1:4:0 → 0:1:0 → 0:10:1) afforded the targeted 3-amino 1,2,4-benzothiadiazine 1,1-dioxide **5**.

Acknowledgements

Fonds der Chemischen Industrie e.V. (Kekulé scholarship) and Friedrich-Ebert-Stiftung (Promotionsförderung) are acknowledged for supporting the doctoral studies of RH. The authors thank Benjamin James Statham (RWTH Aachen University) for critical proof reading and fruitful discussion. We thank Mrs. Susanne Pohlman for her support with the synthesis of starting materials, Marcus Frings for the measurement and analysis of HPLC samples, and Dr. Wolfgang Bettray for MS analyses and helpful discussion (all three RWTH Aachen University). In addition, we acknowledge the Alexander von Humboldt Foundation for support of K. R. (AvH research award).

References

[1] For a general overview, see: a) K. A. Scott, J. T. Njardarson, *Top. Curr. Chem.* **2018**, *376*, 5; b) S. Mondal, S. Malakar, *Tetrahedron* **2020**, *76*, 131662; c) C. Zhao, K. P. Rakesh, L. Ravidar, W.-Y. Fang, H.-L. Qin, *Eur. J. Med. Chem.* **2019**, *162*, 679–734; d) M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chem.* **2016**, *16*, 1200–1216; e) S. Apaydın, M. Török, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2042–2050; f) A. Ovung, J. Bhattacharyya, *Biophys. Rev. Lett.* **2021**, *13*, 259–272; g) A. Kołaczek, I. Fusiarz, J. Ławecka, D. Branowska, *Chemik* **2014**, *68*, 620–628.

[2] a) L. Carone, S. G. Oxberry, R. Twycross, S. Charlesworth, M. Mihalyo, A. Wilcock, *J. Pain Symptom Manage.* **2016**, *52*, 144–150; b) K. Sturm, W. Siedel, R. Weyer, H. Ruschig, *Chem. Ber.* **1966**, *99*, 328–344.

[3] a) F. C. Novello, J. M. Sprague, *J. Am. Chem. Soc.* **1957**, *79*, 2028–2029; b) F. C. Novello (Merck & Co., Inc.), US2809194, **1957**; c) A. A. Rubin, F. E. Roth, M. M. Winbury, J. G. Topliss, M. H. Sherlock, N. Sperner, J. Black, *Science* **1961**, *133*, 2067; d) K. H. Beyer, *Br. J. Clin. Pharmacol.* **1982**, *13*, 15–24.

[4] World Health Organization, "World Health Organization model list of essential medicines: 22nd list (2021)", can be found under https://apps.who.int/iris/handle/10665/345533 (accessed July16, 2023).

[5] For a general overview, see: a) Modern Crop Protection Compounds, Volume 1: Herbicides, 3rd ed., (Eds.: P. Jeschke, M. Witschel, W. Krämer, U. Schirmer), Wiley-VCH, Weinheim, **2019**; b) Modern Crop Protection Compounds, Volume 2: Fungicides, 3rd ed., (Eds.: P. Jeschke, M. Witschel, W. Krämer, U. Schirmer), Wiley-VCH, Weinheim, 2019; c) Modern Crop Protection Compounds, Volume 3: Insecticides, 3rd ed., (Eds.: P. Jeschke, M. Witschel, W. Krämer, U. Schirmer), Wiley-VCH, Weinheim, **2019**; d) P. Devendar, G.-F. Yang, *Top. Curr. Chem.* **2017**, *375*, 82.

[6] S. Pazenok, M. J. Ford, G. Schlegel (Bayer Cropscience GmbH), EP1491527, **2004**.

[7] a) S. Debnath, S. Mondal, *Eur. J. Org. Chem.* **2018**, 933–956; b) K. C. Majumdar, S. Mondal, *Chem. Rev.* **2011**, *111*, 7749–7773; c) M. Yu Moskalik, *Molecules* **2023**, *28*, 51.

[8] a) R. Paulissian, *Int. Anesthesiol. Clin.* **1978**, *16*, 201–238; b) J. G. Topliss, S. Nathan, A. A. Rubin (Schering Corporation), US2986573, **1961**; c) J. Black, *Ann. N. Y. Acad. Sci.* **1968**, *150*, 194–203.

[9] S. Chhabra, K. Shah, *Med. Chem. Res.* **2021**, *30*, 15–30.

[10] Selected examples: a) B. I. Huwaimel, M. Bhakta, C. A. Kulkarni, A. S. Milliken, F. Wang, A. Peng, P. S. Brookes, P. C. Trippier, *ChemMedChem* **2021**, *16*, 1143–1162; b) C. Constant-Urban, M. Charif, E. Goffin, J.-C. Van Heugen, B. Elmoualij, P. Chiap, A. Mouithys-Mickalad, D. Serteyn, P. Lebrun, B. Pirotte, P. De Tullio, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5878–5881; c) S. Khelili, G. Leclerc, G. Faury, J. Verdetti, *Bioorg. Med. Chem.* **1995**, *3*, 495–503; d) A. J. Peat, C. Townsend, J. F. Worley, III, S. H. Allen, D. Garrido, R. J. Mertz, J. L. Pfohl, C. M. Terry, J. F. Truax, R. L. Veasey, S. A. Thomson, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2977–2980; e) P. de Tullio, B. Pirotte, P. Lebrun, J. Fontaine, L. on Dupont, M.-H. Antoine, R. Ouedraogo, S. Khelili, C. Maggetto, B. Masereel, O. Diouf, T. Podona, J. Delarge, *J. Med. Chem.* **1996**, *39*, 937–948; f) S. Boverie, M.-H. Antoine, P. de Tullio, F. Somers, B. Becker, S. Sebille, P. Lebrun, B. Pirotte, *J. Pharm. Pharmacol.* **2001**, *53*, 973–980; g) B. Pirotte, P. de Tullio, Q.-A. Nguyen, F. Somers, P. Fraikin, X. Florence, P. Wahl, J. Bondo Hansen, P. Lebrun, *J. Med. Chem.* **2010**, *53*, 147–154; h) S. Boverie, M.-H. Antoine, F. Somers, B. Becker, S. Sebille, R. Ouedraogo, S. Counerotte, B. Pirotte, P. Lebrun, P. de Tullio, *J. Med. Chem.* **2005**, *48*, 3492–3503; i) B. Pirotte, P. de Tullio, P. Lebrun, M.-H. Antoine, J. Fontaine, B. Masereel, M. Schynts, L. Dupont, A. Herchuelz, J. Delarge, *J. Med. Chem.* **1993**, *36*, 3211–3213; j) P. de Tullio, B. Becker, S. Boverie, M. Dabrowski, P. Wahl, M.-H. Antoine, F. Somers, S. Sebille, R. Ouedraogo, J. Bondo Hansen, P. Lebrun, B. Pirotte, *J. Med. Chem.* **2003**, *46*, 3342–3353; k) B. Pirotte, P. de Tullio, S. Boverie, C. Michaux, P. Lebrun,

J. Med. Chem. **2011**, *54*, 3188–3199; l) P. de Tullio, A.-C. Servais, M. Fillet, F. Gillotin, F. Somers, P. Chiap, P. Lebrun, B. Pirotte, *J. Med. Chem.* **2011**, *54*, 8353–8361; m) R. Tedesco, A. N. Shaw, R. Bambal, D. Chai, N. O. Concha, M. G. Darcy, D. Dhanak, D. M. Fitch, A. Gates, W. G. Gerhardt, D. L. Halegoua, C. Han, G. A. Hofmann, V. K. Johnston, A. C. Kaura, N. Liu, R. M. Keenan, J. Lin-Goerke, R. T. Sarisky, K. J. Wiggall, M. N. Zimmerman, K. J. Duffy, *J. Med. Chem.* **2006**, *49*, 971–983; n) P. de Tullio, S. Boverie, B. Becker, M.-H. Antoine, Q.-A. Nguyen, P. Francotte, S. Counerotte, S. Sebille, B. Pirotte, P. Lebrun, *J. Med. Chem.* **2005**, *48*, 4990–5000; o) M. Wenzel, M. E. Light, A. P. Davis, P. A. Gale, *Chem. Commun.* **2011**, *47*, 7641–7643; p) P. Lebrun, P. Arkhammar, M.-H. Antoine, Q.-A. Nguyen, J. Bondo Hansen, B. Pirotte, *Diabetologia* **2000**, *43*, 723–732.

[11] a) Z. Segaoula, J. Leclercq, V. Verones, N. Flouquet, M. Lecoeur, L. Ach, N. Renault, A. Barczyk, P. Melnyk, P. Berthelot, X. Thuru, N. Lebegue, *J. Med. Chem.* **2016**, *59*, 8422–8440; b) R. Ouedraogo, B. Becker, S. Boverie, F. Somers, M.-H. Antoine, B. Pirotte, P. Lebrun, P. de Tullio, *Biol. Chem.* **2002**, *383*, 1759–1768; c) J.-W. Chern, P.-L. Tao, K.-C. Wang, A. Gutcait, S.-W. Liu, M.-H. Yen, S.-L. Chien, J.-K. Rong, *J. Med. Chem.* **1998**, *41*, 3128–3141; d) A. V. N. Reddy, A. Kamal, A. B. Rao, P. B. Sattur, *Eur. J. Med. Chem.* **1987**, *22*, 157–160.

[12] a) T. Inokuma, M. Furukawa, T. Uno, Y. Suzuki, K. Yoshida, Y. Yano, K. Matsuzaki, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 10470–10477; b) Y. Kobayashi, R. Kuramoto, Y. Takemoto, *Beilstein J. Org. Chem.* **2015**, *11*, 2654–2660; c) T. Nanjo, X. Zhang, Y. Tokuhiro, Y. Takemoto, *ACS Catal.* **2019**, *9*, 10087–10092; d) Y. Tokuhiro, K. Yoshikawa, S. Murayama, T. Nanjo, Y. Takemoto, *ACS Catal.* **2022**, *12*, 5292–5304; e) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, *Angew. Chem. Int. Ed.* **2013**, *52*, 11114–11118; *Angew. Chem.* **2013**, *125*, 11320–11324; f) Y. Kobayashi, S. Li, Y. Takemoto, *Asian J. Org. Chem.* **2014**, *3*, 403–407; g) T. Inokuma, M. Furukawa, Y. Suzuki, T. Kimachi, Y. Kobayashi, Y. Takemoto, *ChemCatChem* **2012**, *4*, 983–985.

[13] a) C. Blackburn, A. Achab, A. Elder, S. Ghosh, J. Guo, G. Harriman, M. Jones, *J. Org. Chem.* **2005**, *70*, 10206–10209; b) S. Hirota, R. Kato, M. Suzuki, Y. Soneta, T. Otani, T. Saito, *Eur. J. Org. Chem.* **2008**, 2075–2083; c) S. Hirota, T. Sakai, N. Kitamura, K. Kubokawa, N. Kutsumura, T. Otani, T. Saito, *Tetrahedron* **2010**, *66*, 653–662; d) L. H. Pettus, K. L. Andrews, S. K. Booker, J. Chen, V. J. Cee, F. Chavez Jr., Y. Chen, H. Eastwood, N. Guerrero, B. Herberich, D. Hickman, B. A. Lanman, J. Laszlo, M. R. Lee, J. R. Lipford, B. Mattson, C. Mohr, Y. Nguyen, M. H. Norman, D. Powers, A. B. Reed, K. Rex, C. Sastri, N. Tamayo, P. Wang, J. T. Winston, B. Wu, T. Wu, R. P. Wurz, Y. Xu, Y. Zhou, A. S. Tasker, H.-L. Wang, *J. Med. Chem.* **2016**, *59*, 6407–6430.

[14] a) J.-W. Chern, J.-G. Rong, *Tetrahedron Lett.* **1991**, *32*, 2935–2938; b) N. P. Peet, S. Sunder, R. J. Barbuch, E. W. Huber, E. M. Bargar, *J. Heterocycl. Chem.* **1987**, *24*, 1531–1535; c) J.-W. Chern, C.-P. Ho, Y.-H. Wu, J.-G. Rong, K.-C. Liu, *J. Heterocycl. Chem.* **1990**, *27*, 1909–1915; d) J.-W. Chern, Y.-H. Wu, K.-C. Liu, *J. Heterocycl. Chem.* **1990**, *27*, 1485–1488; e) A. Cherepakha, V. O. Kovtunenko, A. Tolmachev, O. Lukin, K. G. Nazarenko, *Synth. Commun.* **2011**, *41*, 1977–1989; f) C. McMaster, V. Fülöpová, I. Popa, M. Grepl, M. Soural, *ACS Comb. Sci.* **2014**, *16*, 221–224.

[15] a) G. Wittig, G. Geissler, *Liebigs Ann. Chem.* **1953**, *580*, 44–57; b) P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev.* **2013**, *42*, 6670–6696; c) K. Pedrood, M. N. Montazer, B. Larijani, M. Mahdavi, *Synthesis* **2021**, *53*, 2342–2366; d) S. Eguchi, Y. Matsushita, K. Yamashita, *Org. Prep. Proced. Int.* **1992**, *24*, 209–243.

[16] a) J.-W. Chern, C.-P. Ho, Y.-H. Wu, C.-Y. Shiau, M.-H. Yen, K.-C. Liu, *Chin. Pharm. J.* **1990**, *42*, 233–238; b) A. A. Shalimov, T. I. Chudakova, Y. G. Vlasenko, A. D. Sinitsa, P. P. Onys'ko, *Chem. Heterocycl. Compd.* **2016**, *52*, 267–274; c) A. Cherepakha, V. O. Kovtunenko, A. Tolmachev, *Tetrahedron Lett.* **2013**, *54*, 986–988; d) D. Innes, M. V. Perkins, A. J. Liepa, C. L. Francis, *Aust. J. Chem.* **2018**, *71*, 610–623; e) P. B. Dalvi, K.-L. Lin, M. V. Kulkarni, C.-M. Sun, *Org. Lett.* **2016**, *18*, 3706–3709.

[17] For recent overviews on isocyanides, see: a) A. Massarotti, F. Brunelli, S. Aprile, M. Giustiniano, G. C. Tron, *Chem. Rev.* **2021**, *121*, 10742–10788; b) P. Patil, M. Ahmadian-Moghaddam, A. Dömling, *Green Chem.* **2020**, *22*, 6902–6911.

[18] a) J. Escudero, P. Mampuys, C. Mensch, C. B. Bheeter, R. Vroemans, R. V. A. Orru, J. Harvey, B. U. W. Maes, *ACS Catal.* **2022**, *12*, 6857–6873; b) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chem. Int. Ed.* **2012**, *51*, 13058–13061; *Angew. Chem.* **2012**, *124*, 13235–13238.

[19] a) R. Hommelsheim, S. Bausch, R. van Nahl, J. S. Ward, K. Rissanen, C. Bolm, *Green Chem.* **2023**, *25*, 3021–3026; b) R. Hommelsheim, H. M. Núñez Ponce, K. – N Truong, K. Rissanen, C. Bolm, *Org. Lett.* **2021**, *23*, 3415–3420; c) A. Isor, R. Hommelsheim, G. W. Cone, M. Frings, J. T. Petroff II, C. Bolm, R. D. McCulla, *Photochem. Photobiol.* **2021**, *97*, 1322–1334; d) D. Ma, D. Kong, C. Wang, K.-N. Truong, K. Rissanen, C. Bolm, *Org. Lett.* **2021**, *23*, 8287–8290; e) R. Hommelsheim, S. Bausch, A. Selvakumar, M. M. Amer, K.-N. Truong, K. Rissanen, C. Bolm, *Chem. Eur. J.* **2023**, *29*, e202203729; f) X. Wang, K. Rissanen, C. Bolm, *Org. Lett.* **2023**, *25*, 1569–1572; g) P. Wu, J. Ward, K. Rissanen, C. Bolm, *Adv. Synth. Catal.* **2023**, *365*, 522–526.

[20] a) Z.-L. Ren, H.-H. Kong, W.-T. Lu, M. Sun, M.-W. Ding, *Tetrahedron* **2018**, *74*, 184–193; b) A. J. Ansari, R. S. Pathare, A. K. Maurya, V. K. Agnihotri, S. Khan, T. K. Roy, D. M. Sawant, R. T. Pardasani, *Adv. Synth. Catal.* **2018**, *360*, 290–297; c) Z. Zhang, P. Tan, W. Chang, Z. Zhang, *Adv. Synth. Catal.* **2021**, *363*, 5344–5359; d) J. W. Collet, T. R. Roose, B. Weijers, B. U. W. Maes, E. Ruijter, R. V. A. Orru, *Molecules* **2020**, *25*, 4906; e) T. R. Roose, D. S. Verdoorn, P. Mampuys, E.

Ruijter, B. U. W. Maes, R. V. A. Orru, *Chem. Soc. Rev.* **2022**, *51*, 5842–5877.
[21] e-EROS, "Bis(dibenzylideneacetone)palladium(0)", can be found under https://onlinelibrary.wiley.com/doi/10.1002/047084289X.rb138.pub3 (accessed: July 16, 2023).
[22] A comprehensive list on the optimization of the reaction conditions can be found within the Supporting Information.
[23] For details, see the Supporting Information.
[24] K. Kumar, *ChemistrySelect* **2020**, *5*, 10298–10328.
[25] The molecular structures for compound **1a** (CCDC 2287535), **3aa** (CCDC 2287537), **3ab** (CCDC 2287538), **3ak** (CCDC 2287539), and **5aa** (CCDC 2287536) were determined by X-ray crystallographic analyses. The corresponding physical data can be found in the Supporting Information or on the website of the joint Cambridge Crystallographic Data Centre by using the respective CCDC number.
[26] Applying the protocol developed in Scheme 3, compound **3ga** was isolated in 53% yield using 5.0 mol% $Pd(dba)_2$.
[27] Cs_2CO_3 has previously been used for consecutive functionalizations in palladium-catalyzed reactions of azides with isocyanides. See ref. 20a or Z. Zhang, Z. Li, B. Fu, Z. Zhang, *Chem. Commun.* **2015**, *51*, 16312–16315.
[28] The addition of Cs_2CO_3 (1.0 equiv.) in the reaction of azide **1a** and isocyanide **2a** had no positive influence on the yield of the reaction or the catalyst loading. For more details, see the Supporting Information.
[29] At this stage, the role of trace amounts of palladium cannot be ruled out completely.
[30] For general remarks on the safe handling of azides, see: a) Organic Azides: Syntheses and Applications, Vol. 1 (Eds.: S. Bräse, K. Banert), John Wiley & Sons, Ltd, Chichester, **2010**; b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188–5240; *Angew. Chem.* **2005**, *117*, 5320–5374; c) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075; d) D. S. Treitler, S. Leung, *J. Org. Chem.* **2022**, *87*, 11293–11295; e) F. Gonzaĺez-Bobes, N. Kopp, L. Li, J. Deerberg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm, M. Hrytsak, *Org. Process Res. Dev.* **2012**, *16*, 2051–2057.

Palladium-Catalyzed Domino Reaction for the Synthesis of 3-Amino 1,2,4-Benzothiadiazine 1,1-Dioxides

Adv. Synth. Catal. **2023**, *365*, 1–9

R. Hommelsheim, R. van Nahl, L. M. Hanek, J. S. Ward, K. Rissanen, C. Bolm*