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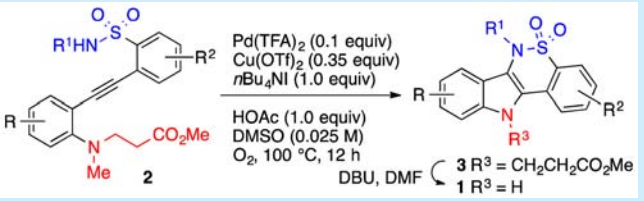
Sulfonamide and Tertiary Amine as Nucleophiles in Pd(II)-Catalyzed Diamination of Alkynes: Synthesis of Tetracyclic Indolobenzothiazine *S,S*-Dioxides

Tu M. Ha, Bo Yao, Qian Wang, and Jieping Zhu*

Laboratory of Synthesis and Natural Products, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne, EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne, Switzerland

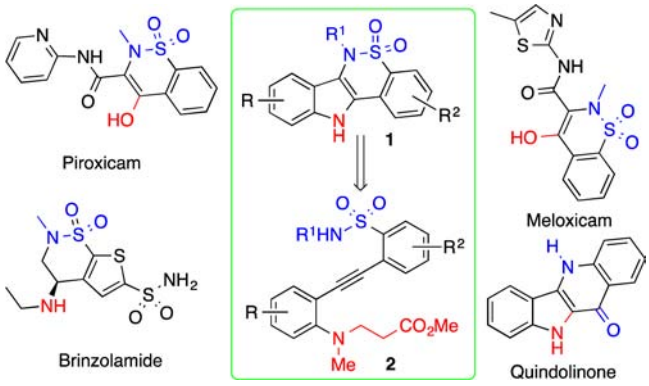
Supporting Information

ABSTRACT: Pd(II)-catalyzed oxidative double cyclization of the 1,2-diarylethynes bearing an *N*-methyl-*N*-(2-methoxycarbonyl)ethylamino and an aminosulfonyl group afforded indolobenzothiazine *S,S*-dioxides in good to excellent yields. The 2-(methoxycarbonyl)ethyl group attached to the indolyl nitrogen is readily removed under basic conditions (DBU, DMF, 120 °C) to provide the corresponding tetracycles with a free indolyl nitrogen in excellent yields.



Sulfonamides and particularly sultams are important substructures in medicinal chemistry.[1] For example, 1,2-benzothiazine *S,S*-dioxide is a pharmacophore found in a number of marketed anti-inflammatory drugs such as meloxicam, piroxicam, and brinzolamide (Scheme 1).[2] Therefore, the development of new synthetic methodology to access this heterocycle has attracted much recent attention.[3] As a continuation of our interest in the development of Pd(II)-catalyzed double nucleophilic addition to alkynes,[4,5] we became interested in the difunctionalization of alkynes involving sulfonamide and aniline as internal nucleophiles. We report herein the synthesis of indolobenzothiazine *S,S*-dioxides **1** featuring a key double cyclization of sulfonamide-containing alkynes **2** (Scheme 1). The tetracycles **1** could be considered analogues of the aforementioned drugs and of quindolinone, a representative member of natural indoloquinolone with diverse biological activities such as antimalarial, antimuscarine, antibacterial, antiviral, antiplasmodial, antihypoglycemic, and PARPs inhibitory activities.[6]

Scheme 1. Natural Product (Quidolinone) and Drugs Having 1,2-Benzothiazine *S,S*-Dioxide Structural Motif



Palladium-catalyzed diamination[7] of alkenes has attracted much attention in recent years.[8] Interestingly, the corresponding diamination of alkynes has been far less studied,[9] and bis-nucleophilic addition across alkynes involving aniline and sulfonamide nitrogen is, to the best of our knowledge, unknown. We began our studies using *N*-phenyl sulfonamide **2a** as a test substrate (Table 1). The desired indolobenzothiazine *S,S*-dioxide **3a** was indeed obtained, albeit in moderate yield (42%), when **2a** was submitted to the conditions optimized for the benzamide counterpart (entry 1). Since using $Pd(OAc)_2$ as a catalyst led to a nonselective *N*-dealkylation process, $Pd(TFA)_2$ was kept as a palladium source in our survey of reaction conditions. As it is seen from Table 1, replacing HOAc by triflic acid (entry 2) or performing the reaction in the absence of $Cu(OTf)_2$ produced only a negligible amount of product (entries 3, 4). Among the copper salts screened, $Cu(OTf)_2$ provided a better result than $Cu(OAc)_2$, $CuCl_2$, and CuI (entries 5−8). Further survey of the reaction conditions indicated that the reaction outcome was very sensitive to the stoichiometry of $Pd(TFA)_2$ and $Cu(OTf)_2$, the reaction temperature, and the oxidant (entries 9−17). The optimum conditions consisted of heating a DMSO solution (*c* 0.025 M) of **2a** to 100 °C in the presence of $Pd(TFA)_2$ (0.1 equiv), $Cu(OTf)_2$ (0.35 equiv), nBu_4NI (1.0 equiv), and HOAc (1.0 equiv) under an oxygen atmosphere. Under these conditions, tetracycle **3a** was isolated in 75% yield. A higher or lower loading of $Cu(OTf)_2$ led to a diminished yield of **3a** (entry 12 vs entries 14, 15), and running the reaction at 100 °C was optimum (entries 11−13). Better results were obtained

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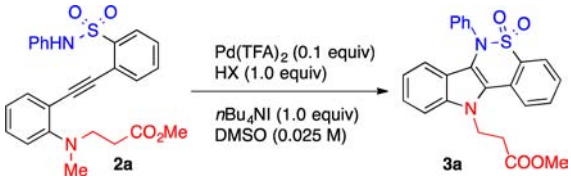
Table 1. Conditions Survey for the Intramolecular Oxidative Diamination of 2a[a]



entry	[Cu] (equiv)	HX	t (°C)	t (h)	[ox]	yield (%)[b]
1	$Cu(OTf)_2$ (0.25)	HOAc	80	13	air	42
2	$Cu(OTf)_2$ (0.25)	HOTf	80	21	air	<10
3	–	HOAc	80	21	air	<5
4	–	HOTf	80	21	air	<5
5	$Cu(OTf)_2$ (1.0)	HOAc	90	12	O_2	27
6	$Cu(OAc)_2$ (1.0)	HOAc	90	12	O_2	0
7	$CuCl_2$ (1.0)	HOAc	90	12	O_2	25
8	CuI (1.0)	HOAc	90	12	O_2	13
9	$Cu(OTf)_2$ (0.35)	HOAc	65	12	O_2	31
10	$Cu(OTf)_2$ (0.35)	HOAc	80	12	O_2	62
11	$Cu(OTf)_2$ (0.35)	HOAc	90	12	O_2	65
12	**$Cu(OTf)_2$ (0.35)**	**HOAc**	**100**	**12**	**O_2**	**76 (75)**
13	$Cu(OTf)_2$ (0.35)	HOAc	110	12	O_2	59
14	$Cu(OTf)_2$ (0.25)	HOAc	100	12	O_2	34
15	$Cu(OTf)_2$ (0.45)	HOAc	100	12	O_2	49
16[c]	$Cu(OTf)_2$ (0.35)	HOAc	100	12	O_2	42
17	$Cu(OTf)_2$ (0.35)	HOAc	100	12	air	56

[a]Reaction conditions: **2a** (0.05 mmol), $Pd(TFA)_2$ (0.1 equiv), HX (1.0 equiv), nBu$_4$NI (1.0 equiv) in DMSO (2.0 mL). [b]Yield determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. Isolated yield in parentheses. [c]Pd(OTf)2 (0.05 equiv) was used.

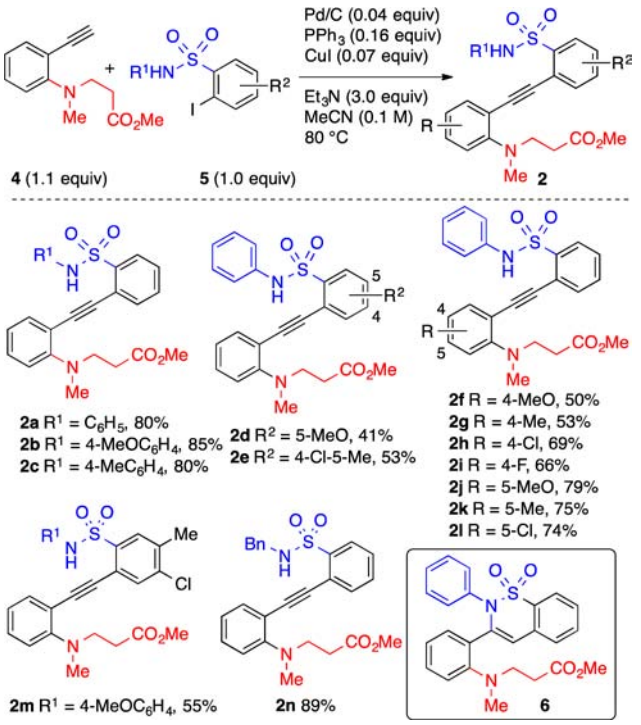
when the reaction was carried out under oxygen instead of an air atmosphere (entry 12 vs 17).[10,11]

With the optimum conditions in hand, the substrate scope was next examined. Synthesis of substituted 2-[(2-aminophenyl)ethynyl]benzenesulfonamides **2** is shown in Scheme 2. Coupling of **4a** (R = H) and **5a** (R^1 = Ph, R^2 = H) under standard Sonogashira conditions afforded mainly the monocyclized product **6** [$Pd(PPh_3)_2Cl_2$ (0.03 equiv), CuI (0.04 equiv), Et_3N (4.0 equiv), DMF (0.2 M), 80 °C].[12] The higher acidity of the sulfonamide NH moiety in **2a** might be responsible for the observed facile cyclization. After screening of different reaction conditions, Pal's conditions [Pd/C (0.04 equiv), PPh_3 (0.16 equiv)), CuI (0.07 equiv), Et_3N (3.0 equiv) in MeCN (0.1 M) at 80 °C][3e] were found to be optimum for this coupling reaction. Under these conditions, various terminal alkynes **4** coupled efficiently with 2-iodobenzenesulfonamides **5** to furnish **2** in good to excellent yields (Scheme 2).

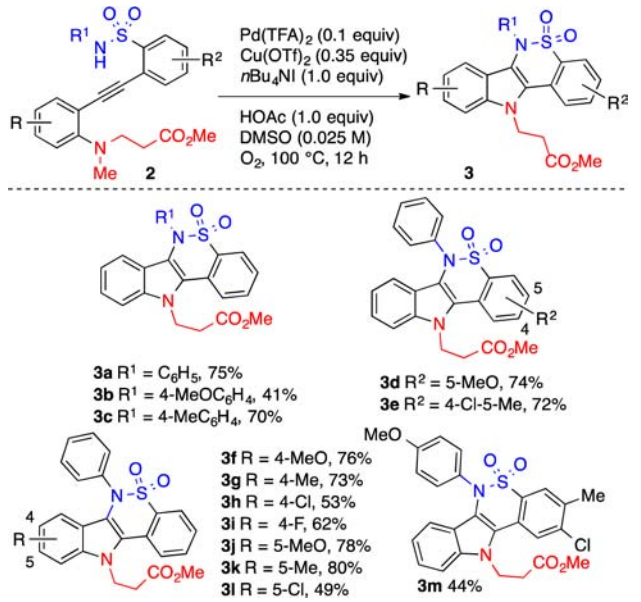
The results of Pd-catalyzed oxidative diamination are summarized in Scheme 3. As it is seen, no significant electronic effect was observed and the presence of both electron-donating and -withdrawing groups in all three aromatic rings is well tolerated. As expected, aryl chloride is inert under these conditions providing compounds with a handle for further functionalization. However, the *N*-benzylsulfonamide **2n** failed to undergo the double cyclization under these conditions.

Removal of the *N*-(2-methoxycarbonyl)ethyl group by way of the retro-aza-Michael reaction was next investigated. Gratefully, simply heating a DMF solution of **3a** in the presence of DBU (1.0 equiv) at 120 °C afforded the desired *N*-deprotection product **1a** in 93% yield.[4f] These conditions were found to be

Scheme 2. Synthesis of Sulfonamides 2



Scheme 3. Indole-Fused Benzothiazine *S,S*-Dioxides 3: Scope



generally applicable to a wide range of substrates as it is summarized in Scheme 4.

A possible catalytic cycle was proposed as shown in Scheme 5. Coordination of both alkyne and sulfonamide to Pd(II) species followed by deprotonation of the sulfonamide NH would afford σ,π-chelated palladium complex **A**. An *anti*-aminopalladation involving the tethered tertiary amine to the triple bond via a 5-*endo*-dig mode would afford the σ-indolylpalladium(II) complex **B**,[4,13] which upon reductive elimination would produce ammonium salt **C** and Pd(0).[14] Chemoselective S_N2 attack of iodide on the *N*-methyl group would provide the tetracyclic product **3**. Finally, oxidation of

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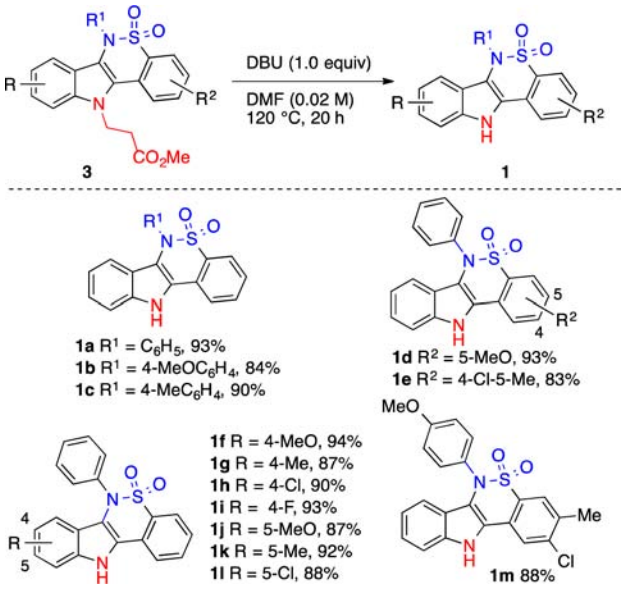
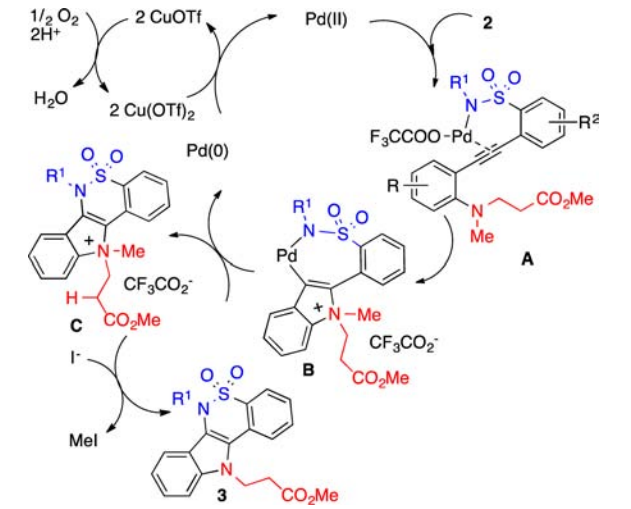
Scheme 4. *N*-Deprotection of Tetracycles 3 by the Retro-aza-Michael Addition



Scheme 5. Possible Reaction Pathway



Pd(0) to Pd(II) by Cu(II) salt completed the catalytic cycle. It is worth noting that ^{1}H NMR titration of **2a** in DMSO-d_6 with HOAc indicated that the *N*,*N*-dimethylamino group was not protonated under these conditions.[15] To gain insight into this mechanistic proposal, isolation of one of the proposed intermediates was attempted. Gratefully, reaction of **2a** with Pd(TFA)$_2$ (1.0 equiv) in DMSO-d_6 at room temperature for 45 min afforded a compound whose spectroscopic data are in agreement with the σ-vinyl palladium complex **B** (*cf.* Supporting Information). Intermediate **B**, stable at room temperature, was converted to **3a** upon heating in DMSO indicating that **B** could indeed be an intermediate in the conversion of **2** to **3**. This control experiment also indicated that the diamination of **2** leading to **3** proceeded through the Pd(II)/Pd(0) catalytic cycle.

In conclusion, we reported a novel Pd(II)-catalyzed intramolecular diamination of alkynes involving tertiary amine and sulfonamide as internal nucleophiles. The 1,2-diarylethynes bearing an *N*-methyl-*N*-(2-methoxycarbonyl)ethylamino and an aminosulfonyl group readily cyclized to afford indolobenzothiazine *S*,*S*-dioxides in good to excellent yields. In addition, the present work further demonstrated the utility of 2-(methoxycarbonyl)ethyl as an *N*-protective group of indoles since it is inert under the cyclization conditions but is readily removed under basic conditions (DBU, DMF, 120 °C) affording the corresponding tetracycles **1** with a free indolyl nitrogen in excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02621.

Experimental procedures, product characterization data, ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jieping.zhu@epfl.ch.

Notes

The authors declare no competing financial interest.

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(14) The hypothesis that reductive elimination occurred before the N-dealkylation step is based on our mechanistic studies on the cyclizative alkynylation reaction under similar reaction conditions; see ref 4d.

(15) The pK_{aH} of $ArNMe_2H^+$: 5.2 in water, 2.5 in DMSO. The pK_a of AcOH: 4.76 in water, 12.3 in DMSO. Therefore, we can estimate that only a tiny amount of **2** in DMSO will be protonated in accordance with this ^{1}H NMR titration experiment.

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