ACS Combinatorial Science

Research Article

pubs.acs.org/acscombsci

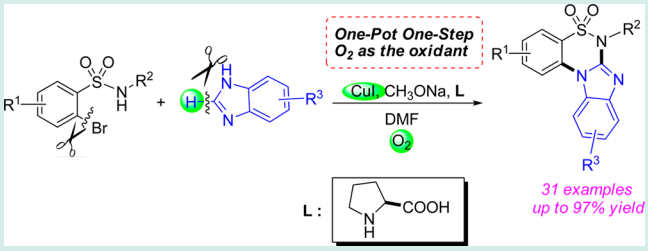
Copper-Catalyzed Domino Synthesis of Nitrogen Heterocycle-Fused Benzoimidazole and 1,2,4-Benzothiadiazine 1,1-Dioxide Derivatives

Daoshan Yang, Baojuan An, Wei Wei, Laijin Tian, Ben Huang, and Hua Wang*

The Key Laboratory of Life-Organic Analysis and Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong China

Supporting Information

ABSTRACT: A convenient copper-catalyzed domino method for the synthesis of nitrogen heterocycle-fused benzoimidazole and 1,2,4-benzothiadiazine 1,1-dioxides has been developed using readily available 2-bromo-*N*-phenylbenzenesulfonamides and benzimidazole derivatives as the starting materials. The domino process comprises an Ullmann-type *N*-arylation and intramolecular C−H amination. The inexpensive and efficient copper-catalyzed method should provide a new and useful strategy for for constructing novel, biologically interesting heterocycles containing benzoimidazole and 1,2,4-benzothiadiazine 1,1-dioxide motifs.



KEYWORDS: *copper-catalyzed, N-heterocycle, domino reaction, benzimidazole, 1,2,4-benzothiadiazine 1,1-dioxide*

N-heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, dyes, and particularly in biologically active molecules. Therefore, the development of novel, practical, and efficient methods for nitrogen-containing heterocyclic synthesis is an important goal in modern organic synthesis. The benzimidazole scaffold, broadly occurring in natural products, shows a variety of biological and medicinal activities. They also can be used as polymers,[1] dyes,[2] drugs[3] and enzyme inhibitors.[4] On the other hand, the 1,2,4-benzothiadiazine 1,1-dioxide ring is a key structure contained in some biologically active molecules.[5] For example, they have been used as potential anticancer agents,[6] and have been shown to possess antiviral activities including against human cytomegalovirus (H-CMV)[7] and human herpesvirus 6 (HHV-6).[8] In addition, some of the benzothiadiazine 1,1-dioxide derivatives have shown excellent biological activity in the treatment of early stages of Alzheimer disease,[9] and they have also been used as "potassium channel openers" (PCOs) that can activate KATP channels.[10] Recently, many methods have been developed for the synthesis of benzothiadiazines.[11] However, to the best of our knowledge, synthesis of the combined motifs of benzimidazole and 1,2,4-benzothiadiazine 1,1-dioxide frameworks (Figure 1) has not been reported thus far. Therefore, we seek to develop an efficient and practical method for the synthesis of this new kind of fused *N*-heterocycles which could possibly possess biological activity.

The C−N bond formation is of fundamental and immense importance in synthetic chemistry because of its wide existence in natural products, biologically active compounds, drug molecules, and materials. Palladium-catalyzed Buchwald−Hartwig coupling is a traditional method to construct aromatic C−N bonds.[12] Recently, considering the ready availability and low toxicity of copper catalysts and their ligands, great progress has been made in copper-catalyzed Ullmann-type C−X (X = N, O, and S) bond formation, and some N-heterocycles were made through such couplings.[13−15] Also, direct formation of various functional groups from inert C−H bonds meets the requirement of atom-economy and has emerged as a powerful tool for organic transformations.[16] Furthermore, for economical and environmental reasons, there is an increasing demand for the use of dioxygen as an ideal oxidant for many oxidation reactions because of its abundance, low cost, and nontoxicity.[17] Some elegant copper-catalyzed approaches have been developed for the synthesis of heterocycles via sp^2 C−H activation/C−N bond-forming strategy using dioxygen as the green oxidant.[18] These works prompted us to seek more efficient methods to construct novel heterocycles with potential biological activity. Herein, we report an efficient copper-catalyzed "One-Pot, One-Step, approach" for the synthesis of benzoimidazo 1,2,4-benzothiadiazine 1,1-dioxide derivatives, a new class of *N*-heterocycles with potential biological activity.

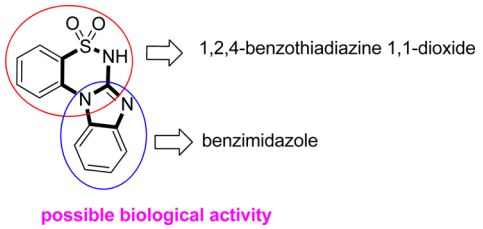
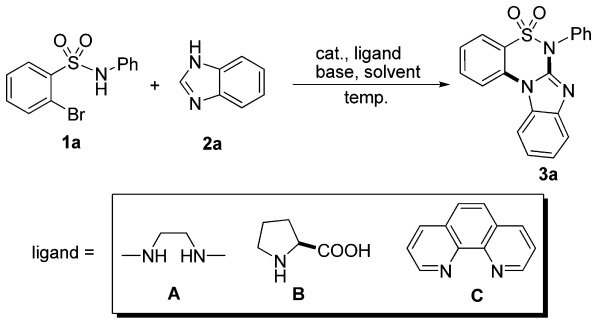


Figure 1. Structure of fused heterocyclic compound containing benzimidazole and 1,2,4-benzothiadiazine 1,1-dioxide frameworks.

Received: August 8, 2014
Revised: December 26, 2014
Published: December 30, 2014

DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119

Table 1. Copper-Catalyzed Coupling of 2-Bromo-*N*-phenylbenzenesulfonamide with 1*H*-Benzo[*d*]imidazole: Optimization of Conditions[a]



entry	cat.	ligand	base	solvent	temp. [°C]	yield [%][b]
1	CuI	A	Cs_2CO_3	DMSO	130	85
2	CuBr	A	Cs_2CO_3	DMSO	130	81
3	$CuCl_2$	A	Cs_2CO_3	DMSO	130	78
4	$Cu(OAc)_2$	A	Cs_2CO_3	DMSO	130	70
5	$CuSO_4$	A	Cs_2CO_3	DMSO	130	75
6	CuI	B	Cs_2CO_3	DMSO	130	87
7	CuI	C	Cs_2CO_3	DMSO	130	80
8	CuI	B	K_2CO_3	DMSO	130	81
9	CuI	B	CH_3ONa	DMSO	130	84
10	**CuI**	**B**	**CH_3ONa**	**DMF**	**130**	**89**
11	CuI	B	CH_3ONa	1,4-dioxane	130	45
12	CuI	B	CH_3ONa	toluene	130	21
13	CuI	B	CH_3ONa	DMF	110	67
14	CuI	B	CH_3ONa	DMF	90	32
15	CuI	B	CH_3ONa	DMF	130	74[c]
16	CuI		CH_3ONa	DMF	130	83

[a]Reaction conditions: 2-bromo-*N*-phenylbenzenesulfonamide **1a** (0.25 mmol), 1*H*-benzo[*d*]imidazole **2a** (0.3 mmol), catalyst (0.05 mmol), ligand (0.05 mmol), base (0.5 mmol), solvent (1 mL). [b]Isolated yield. [c]Under air atmosphere.

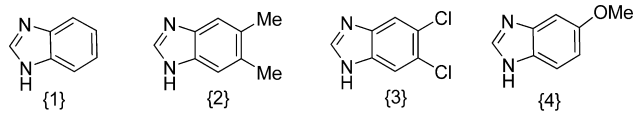


Figure 3. 1*H*-benzo[*d*]imidazoles tested in the study (chemset **2**).

In order to obtain optimal catalysis conditions, we screened various catalysts, ligands, bases and solvents under a dioxygen atmosphere using 2-bromo-*N*-phenylbenzenesulfonamide and 1*H*-benzo[*d*]imidazole as the model substrates. As shown in Table 1, the copper salts, CuI, CuBr, $CuCl_2$, $Cu(OAc)_2$ and $CuSO_4$ (20 mol % amount relative to 2-bromo-*N*-phenylbenzenesulfonamide), were tested in DMSO (entries 1−5) using 20 mol % *N*, *N*′-dimethylethylenediamine as the ligand and 2 equiv of Cs_2CO_3 as the base at 130 °C. CuI was found to be the most effective catalyst (entry 1). We attempted to use different ligands, and L-proline showed greated activity which had been widely used in many Ullmann-type couplings (compare entries 1, 6, and 7). The reason should be the chelation of Cu(I) with L-proline made Cu(I) species more reactive or stabilized the oxidative addition intermediates (see Scheme 2 formation mechanism) in the transformation based on its steric hindrance reported by Ma and co-workers.[19] The affect of bases was investigated, and CH_3ONa provided the highest efficiency (compare entries 7−9). We screened two aprotic, polar solvents and DMF was slightly better than DMSO (compare entries 9−12). The reaction can also be performed under air atmosphere, and afforded the desired product in 74% yield. Interestingly, the target product (**3a**) was obtained in 83% yield in the absence of ligand (entry 16), which implied the existence of an *ortho*-substitutent (see Scheme 2, formation mechanism, the nitrogen atom of $NHSO_2R$ group may coordinate to Cu, which can stabilize the intermediate **B**).[21] Reaction temperatures were also screened and the yield of the target product maximized at 130 °C (compare entries 10, 12−14). After the above optimization, a variety of heterocyles were synthesized under our standard conditions: 20 mol % CuI as the catalyst, 2 equiv

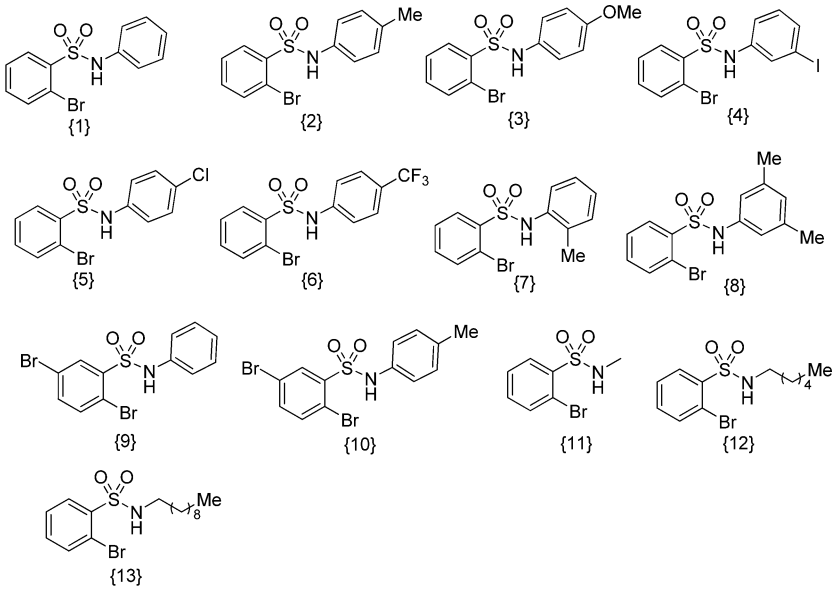
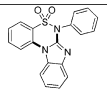
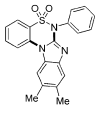
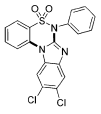
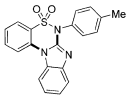
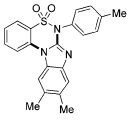
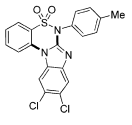
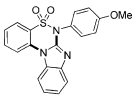
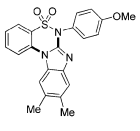
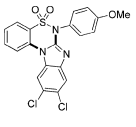
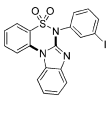
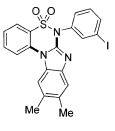
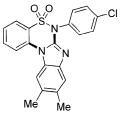
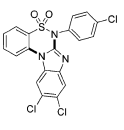
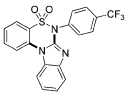
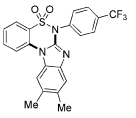
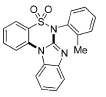
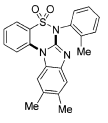
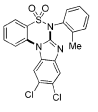
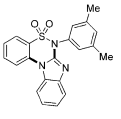
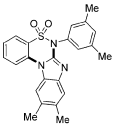
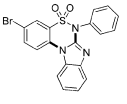
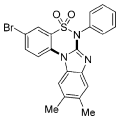
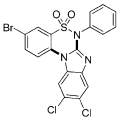
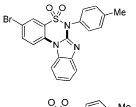
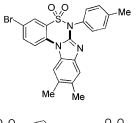
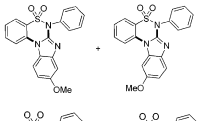
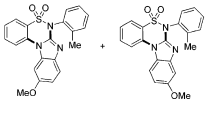


Figure 2. 2-Bromo-*N*-phenylbenzenesulfonamides tested in the study (chemset **1**).

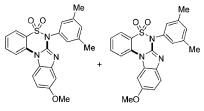
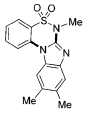
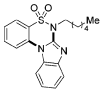
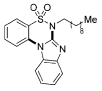
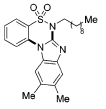
DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119

Table 2. Copper-Catalyzed Synthesis of Benzoimidazo 1,2,4-Benzothiadiazine 1,1-Dioxides Derivatives via Cascade Reactions of Substituted 2-Bromo-*N*-phenylbenzenesulfonamides with 1*H*-Benzo[*d*]imidazoles[ab] (Chemset 3)

Entry		Product	Yield (%)[b]	Yield (%)[b,c]
1	**3**{*1,1*}		89	83
2	**3**{*1,2*}		91	82
3	**3**{*1,3*}		85	74
4	**3**{*2,1*}		94	79
5	**3**{*2,2*}		96	83
6	**3**{*2,3*}		trace	trace
7	**3**{*3,1*}		95	87
8	**3**{*3,2*}		97	88
9	**3**{*3,3*}		23	11
10	**3**{*4,1*}		90	70
11	**3**{*4,2*}		94	86
12	**3**{*5,2*}		88	75
13	**3**{*5,3*}		82	82
14	**3**{*6,1*}		84	79
15	**3**{*6,2*}		88	81
16	**3**{*7,1*}		91	85
17	**3**{*7,2*}		93	90
18	**3**{*7,3*}		34	29
19	**3**{*8,1*}		92	86
20	**3**{*8,2*}		96	93
21	**3**{*9,1*}		85	76
22	**3**{*9,2*}		82	74
23	**3**{*9,3*}		79	66
24	**3**{*10,1*}		91	83
25	**3**{*10,2*}		94	91
26	**3**{*4,1*} and **3**{*4,1*}'		95 (1: 0.87)	92
27	**3**{*7,4*} and **3**{*7,4*}'		92 (1:1)	88

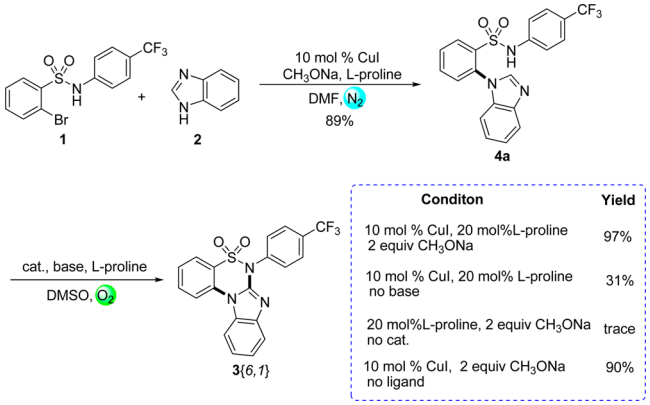
DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119

Table 2. continued

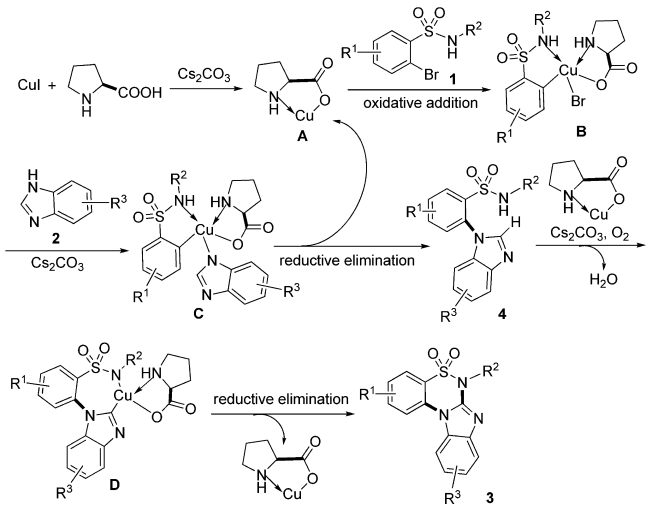
Entry		Product	Yield (%)[b]	Yield (%)[b,c]
28	3{*8,4*} and 3{*8,4*}′		97 (1: 0.47)	91
29	3{*11,2*}		81	75
30	3{*12,1*}		79	67
31	3{*13,1*}		76	66
32	3{*13,2*}		83	73

[a]Reaction conditions: under dioxygen atmosphere, 2-bromo-*N*-phenylbenzenesulfonamide derivative (0.25 mmol), benzimidazoles (0.3 mmol), CuI (0.05 mmol), L-proline (0.05 mmol), CH_3ONa (0.5 mmol), DMF(1 mL). [b]Isolated yield. [c]Without ligand.

Scheme 1. Investigation on Effect of Catalyst, Base, and Ligand for Oxidative Cyclization Reaction



Scheme 2. Possible Formation Mechanism of Benzoimidazo 1,2,4-Benzothiadiazine 1,1-Dioxides



of CH_3ONa as the base, 20 mol % L-proline as the ligand and DMF as the solvent under O_2 atmosphere.

We selected 13 2-bromo-*N*-phenylbenzenesulfonamides (Figure 2) and 4 1*H*-benzo[*d*]imidazoles (Figure 3) from our internal database to test the proposed combination. As shown in Table 2, the scope of substrates was investigated, most of the examined substrates provided the corresponding target products in good to excellent yields. It should be not that, The substrates **1** in which the aromatic amines bearing an electron-donating group showed higher reactivities than those in which it was an electron-withdrawing group (products 3{*1,1*}, 3{*2,1*}, 3{*3,1*}, and 3{*6,1*}), and the substrates **1** containing aryl substituent showed higher reactivity than aliphatic ones (compare entries 3{*1,1*}−3{*8,4*} and 3{*11,2*}−3{*13,2*}). The electron-effect of the substituted groups in 1*H*-benzo[*d*]imidazoles including electron-rich, -deficient, and -neutral groups did not display evidently difference of reactivity. Although this transformation was efficient, unfortunately, not all the benzimidazole derivatives **2** were compatible with 2-bromo-*N*-phenylbenzenesulfonamides **1**. For example, if 5, 6-dichloro-1*H*-benzo[*d*]imidazole chemset **2**{*3*} and 2-bromo-*N*-*p*-tolylbenzenesulfonamide chemset **1**{*2*} were used as the substrates under the optimal reaction conditions, only a trace of product was obtained (Table 2, 3{*2,3*}). The reason might be the electronic effect of the substrates influenced the stability of the transition state. Thus, further investigations to explore more powerful catalyst and ligands was required. Notably, reactions of 2,5-dibromo-*N*-phenylbenzenesulfonamides with 1*H*-benzo-[*d*]imidazoles only took place on the *ortho*-site C−Br bond of the sulfonamide group, the 5-site C−Br bond remained intact, and the result showed the *ortho*-substituent effect of the sulfonamide group during *N*-arylations[19] (products 3{*9,1*}−3{*10,2*}). As expected, unsymmetrical substituted 1*H*-benzo[*d*]imidazole gave a mixture of two regioselective products 3{*4,1*}/3{*4,1*}′ (or 3{*4,1*}′/3{*4,1*}) and 3{*8,4*}/3{*8,4*}′ (or 3{*8,4*}′/3{*8,4*}) in ratios of 1:0.87 and 1:0.47, respectively. Interestingly, when 2-bromo-*N*-*p*-tolylbenzenesulfonamide chemset **1**{*2*} and 6-methoxy-1*H*-benzo[*d*]imidazole chemset **2**{*4*} were used as the substrates, giving a mixture of two regioselective products 3{*7,4*}/3{*7,4*}′ in ratios of 1:1 demonstrating slight steric effects in this transformation. In addition, the cascade reactions could tolerate some functional groups such as methyl ether (products 3{*3,1*}, 3{*3,2*}, and 3{*3,3*}), CF_3 group (products 3{*6,1*} and 3{*6,2*}), C−Cl bond (products 3{*1,3*}, 3{*3,3*}, 3{*5,2*}, and 3{*5,3*}), C−Br bond (products 3{*9,1*}−3{*10,2*}) and C−I bond (products 3{*4,1*} and 3{*4,2*}), which could be used for further modifications at the substituted positions. This reaction was also performed under ligand-free conditions, and it provided the target product in slightly lower yields. However, the experimental procedure of ligand-free conditions was more convenient. Three representative examples are shown in ref 20.

DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119

To understand the mechanism further, we performed some control experiments, with results shown in Scheme 1. First, Copper-catalyzed coupling of **1** with **2** under nitrogen atmosphere provided *N*-arylation product **4a** in 89% yield. Then, intramolecular aerobic oxidative cyclyzation of **4a** under various conditions were investigated. Treatment of **4a** provided **3**{*6,1*} in 97% yield in the presence of 0.1 equiv of CuI, 0.2 equiv of L-proline and 1 equiv of CH_3ONa, while product **3**{*6,1*} was obtained in 31% yield in the absence of CH_3ONa. Yields greatly decreased with reduction of CuI, however, the amount of ligand showed insensitivity.

On the basis of these results above, together with literature reports,[21] we proposed the mechanism in Scheme 2. Reaction of CuI with L-proline produced a five-membered chelate **A**. Oxidative addition of the chelated Cu(I) with substituted 2-bromo-*N*-phenylbenzenesulfonamide (**1**) led to the intermediate **B** stabilized by the $NHSO_2R$ group in which the nitrogen atom may coordinate to Cu. Treatment of 1*H*-benzo[*d*]-imidazole (**2**) in the presence of the base Cs_2CO_3 provided the complex **C**, and then reductive elimination of **C** afforded the *N*-arylation product **4a** and regenerate the chelate **A**. Treatment of **4a** with chelate **A** provided intermediate **D** in the presence of base and dioxygen. Reductive elimination of **D** afforded the target product **3** leaving the catalyst, chelate **A**.

In conclusion, we have developed a simple, practical and efficient copper-catalyzed domino method for the synthesis of the nitrogen heterocycle-fused benzoimidazole and 1,2,4-benzothiadiazine 1,1-dioxide derivatives with potentially biological activities. Some advantages of the protocol involve the use of inexpensive CuI/L-proline as the catalyst/ligand system, readily available substituted 2-bromo-*N*-phenylbenzenesulfonamides and benzimidazole derivatives as the starting materials, and environmentally friendly dioxygen as the sole oxidant. Importantly, the corresponding benzoimidazo 1,2,4-benzothiadiazine 1,1-dioxides were obtained in good to excellent yields. The process is of tolerance toward various functional groups in the substrates, and it should attract much attention in organic chemistry and medicinal chemistry and combinatorial chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^1H and ^{13}C NMR spectra for all compounds is prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +86 537 4458317. Fax: +86 537 4458317. E-mail: huawang_qfnu@126.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21302110, 21302109, and 21375075), the Taishan Scholar Foundation of Shandong Province, the Natural Science Foundation of Shandong Province (ZR2013BQ017 and ZR2013BM007), the Project of Shandong Province Higher Educational Science and Technology Program (J13LD14).

■ REFERENCES

(1) Asensio, J. A.; Gomez-Romero, P. Recent developments on proton conducting poly(2,5-benzimidazole)(ABPBI) membranes for high temperature poly-mer electrolyte membrane fuel cells. *Fuel Cells* **2005**, *5*, 336−343.

(2) Schwartz, G.; Fehse, K.; Pfeiffer, M.; Walzer, K.; Leo, K. Fabrication of two-dimensional coupled photonic crystal resonator arrays by holographic lithography. *Appl. Phys. Lett.* **2006**, *89*, No. 083509.

(3) (a) Fang, B.; Zhou, C. H.; Rao, X. C. Synthesis and biological activities of novel amine-derived bis-azoles as potential antibacterial and antifungal agents. *Eur. J. Med. Chem.* **2010**, *45*, 4388−4398. (b) Ipparaju, S. K.; Joyasawal, T. S.; Pieroni, M.; Kaiser, M.; Brun, R.; Kozikowski, A. P. Pursuit of natural product leads: Synthesis and biological evaluation of 2-[3-hydroxy-2-[(3-hydroxypyridine-2-carbonyl)amino]phenyl]benzoxazole-4-carboxylic acid (A-33853) and its analogues: Discovery of *N*-(2-benzoxazol-2-ylphenyl)benzamides as novel antileishmanial chemotypes. *J. Med. Chem.* **2008**, *51*, 7344−7347. (c) Rida, S. M.; Ashour, F. A.; El-Hawash, S. A. M.; Elsemary, M. M.; Badr, M. H.; Shalaby, M. A. Synthesis of some novel benzoxazole derivatives as anticancer, anti-HIV-1 and antimicrobial agents. *Eur. J. Med. Chem.* **2005**, *40*, 949−959.

(4) (a) White, A. W.; Almassy, R.; Calvert, A. H.; Curtin, N. J.; Griffin, R. J.; Hostomsky, Z.; Maegley, K.; Newell, D. R.; Srinivasan, S.; Golding, B. T. Resistance-modifying agents. 9.[1]Synthesis and biological properties of benzimidazole inhibitors of the dna repair enzyme poly(ADP-ribose) polymerase. *J. Med. Chem.* **2000**, *43*, 4084−4097. (b) Baudy, R. B.; Fletcher, H., III; Yardley, J. P.; Zaleska, M. M.; Bramlett, D. R.; Tasse, R. P.; Kowal, D. M.; Katz, A. H.; Moyer, J. A.; Abou-Gharbia, M. Design, synthesis, SAR, and biological evaluation of highly potent benzimidazole-spaced phosphono-α-amino acid competitive NMDA antagonists of the AP-6 type. *J. Med. Chem.* **2001**, *44*, 1516−1529. (c) Hauel, N. H.; Nar, H.; Priepke, H.; Ries, U.; Stassen, J.; Wienen, W. Structure-based design of novel potent nonpeptide thrombin inhibitors. *J. Med. Chem.* **2002**, *45*, 1757−1766.

(5) Yang, D.; Liu, H.; Yang, H.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. Copper-catalyzed synthesis of 1,2,4-benzothiadiazine 1,1-dioxide derivatives by coupling of 2-halobenzenesulfonamides with amidines. *Adv. Synth. Catal.* **2009**, *351*, 1999−2004.

(6) (a) Martinez, A.; Gil, C.; Abasolo, M. I.; Casto, A.; Bruno, A. M.; Perez, C.; Preto, C.; Otero, J. Benzothiadiazine dioxide dibenzyl derivatives as potent human cytomegalovirus inhibitors: Synthesis and comparative molecular field analysis. *J. Med. Chem.* **2000**, *43*, 3218−3225. (b) Arranz, M. I.; Diaz, J. A.; Ingate, S. T.; Witrrouw, M.; Pannecouque, C.; Balzarini, J.; De Clercq, E.; Vega, S. Synthesis and anti-HIV activity of 1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]-thiadiazines (TTDs): A new family of HIV-1 specific non-nucleoside reverse transcriptase inhibitors. *Bioorg. Med. Chem.* **1999**, *7*, 2811−2822.

(7) Castro, S.; Peromingo, M. T.; Naesens, L.; Andrei, G.; Snoeck, R.; Balzarini, J.; Velázquez, S.; Camarasa, M.-J. 4″-Benzoylureido-TSAO derivatives as potent and selective non-nucleoside HCMV inhibitors. Structure−activity relationship and mechanism of antiviral action. *J. Med. Chem.* **2008**, *51*, 5823−5832.

(8) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. Environmentally friendly iron-catalyzed cascade synthesis of 1,2,4-benzothiadiazine 1,1-dioxide and quinazolinone derivatives. *J. Comb. Chem.* **2009**, *11*, 653−657.

(9) Bliss, T. V. P.; Collingridge, G. L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **1993**, *361*, 31−39.

(10) Boverie, S.; Antoine, M.-H.; Somers, F.; Becker, B.; Sebille, S.; Ouedraogo, R.; Counerotte, S.; Pirotte, B.; Lebrun, P.; Tullio, P. Effect on KATP channel activation properties and tissue selectivity of the nature of the substituent in the 7- and the 3-position of 4*H*-1,2,4-benzothiadiazine 1,1-dioxides. *J. Med. Chem.* **2005**, *48*, 3492−3503.

(11) (a) Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. Synthetic utility of ammonium salts in a Cu-catalyzed three-component reaction as a facile coupling partner. *J. Org. Chem.* **2008**, *73*, 9454−9457. (b) Rolfe, A.; Hanson, P. R. Microwave-assisted sequential one-pot protocol to

DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119

benzothiadiazin-3-one-1,1-dioxides via a copper-catalyzed N-arylation strategy. *Tetrahedron Lett.* **2009**, *50*, 6935−6937. (c) Cherepakha, A.; Kovtunenko, V. O.; Tolmachev, A.; Lukin, O.; Nazarenko, K. G. Facile synthesis of 4*H*-1,2,4-benzothiadiazine-1,1-dioxides. *Synth. Commun.* **2011**, *41*, 1977−1989. (d) Zhao, D.; Zhou, Y.-R.; Shen, Q.; Li, J.-X. Iron-catalyzed oxidative synthesis of N-heterocycles from primary alcohols. *RSC Adv.* **2014**, *4*, 6486−6489.

(12) For reviews, see: (a) Hartwig, J. F. Transition metal catalyzed synthesis of arylamines and aryl ethers from aryl halides and triflates: Scope and mechanism. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. Rational development of practical catalysts for aromatic carbon−nitrogen bond formation. *Acc. Chem. Res.* **1998**, *31*, 805−818.

(13) (a) Rajesh Kumar, M.; Park, A.; Park, N.; Lee, S. Consecutive condensation, C−N and N−N bond formations: A copper-catalyzed one-pot three-component synthesis of 2*H*-indazole. *Org. Lett.* **2011**, *13*, 3542−3545. (b) Martin, R.; Cuenca, A.; Buchwald, S. L. Sequential copper-catalyzed vinylation/cyclization: An efficient synthesis of functionalized oxazoles. *Org. Lett.* **2007**, *9*, 5521−5524. (c) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. Copper-catalyzed synthesis of benzimidazoles via cascade reactions of *o*-haloacetanilide derivatives with amidine hydrochlorides. *J. Org. Chem.* **2008**, *73*, 7841−7844. (d) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. A simple and efficient approach to quinazolinones under mild copper-catalyzed conditions. *Angew. Chem., Int. Ed.* **2009**, *48*, 348−352. (e) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, C. Copper-catalyzed desymmetric intramolecular Ullmann C−N coupling: An enantioselective preparation of indolines. *J. Am. Chem. Soc.* **2012**, *134*, 14326−14329. (f) Martín, R.; Rivero, M. R.; Buchwald, S. L. Domino Cu-catalyzed C−N coupling/hydroamidation: A highly efficient synthesis of nitrogen heterocycles. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079−7082. (g) Zou, B.; Yuan, Q.; Ma, D. Synthesis of 1,2-disubstituted benzimidazoles by a Cu-catalyzed cascade aryl amination/condensation process. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598−2601.

(14) (a) Viirre, R. D.; Evindar, G.; Batey, R. A. Copper-catalyzed domino annulation approaches to the synthesis of benzoxazoles under microwave-accelerated and conventional thermal conditions. *J. Org. Chem.* **2008**, *73*, 3452−3459. (b) Monnier, F.; Taillefer, M. Catalytic C−C, C−N, and C−O Ullmann-type coupling reactions: Copper makes a difference. *Angew.Chem., Int. Ed.* **2008**, *47*, 3096−3099. (c) Nordmann, G.; Buchwald, S. L. A domino copper-catalyzed C−O coupling-Claisen rearrangement process. *J. Am. Chem. Soc.* **2003**, *125*, 4978−4979. (d) Naidu, A. B.; Jaseer, E. A.; Sekar, G. General, mild, and intermolecular Ullmann-type synthesis of diaryl and alkyl aryl ethers catalyzed by diol−copper(I) complex. *J. Org. Chem.* **2009**, *74*, 3675−3679. (e) Monnier, F.; Taillefer, M. Catalytic C−C, C−N, and C−O Ullmann-type coupling reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954−6971.

(15) (a) Lv, X.; Liu, Y.; Qian, W.; Bao, W. Copper(I)-catalyzed one-pot synthesis of 2-iminobenzo-1,3-oxathioles from *ortho*-iodophenols and isothiocyanates. *Adv. Synth. Catal.* **2008**, *350*, 2507−2512. (b) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. Copper-catalyzed synthesis of vinyl sulfides. *Org. Lett.* **2004**, *6*, 5005−5008.

(16) For recent reviews, see: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. Weak coordination as a powerful means for developing broadly useful C−H functionalization reactions. *Acc. Chem. Res.* **2012**, *45*, 788−802. (b) Ackermann, L. Carboxylate-assisted ruthenium-catalyzed alkyne annulations by C−H/Het−H bond functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281−295. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C−H transformation via iron catalysis. *Chem. Rev.* **2011**, *111*, 1293−1314. (d) Neufeldt, S. R.; Sanford, M. S. Controlling site selectivity in palladium-catalyzed C−H bond functionalization. *Acc. Chem. Res.* **2012**, *45*, 936−946. (e) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium catalyzed chelation-assisted C−H bond functionalization reactions. *Acc. Chem. Res.* **2012**, *45*, 814−825.

(17) (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent advances in transition metal catalyzed oxidation of organic substrates with molecular oxygen. *Chem. Rev.* **2005**, *105*, 2329−2364. (b) Kieber-Emmons, M. T.; Riordan, C. G. Dioxygen activation at monovalent nickel. *Acc. Chem. Res.* **2007**, *40*, 618−625. (c) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. Dioxygen-triggered oxidative radical reaction: Direct aerobic difunctionalization of terminal alkynes toward *β*-keto sulfones. *J. Am. Chem. Soc.* **2013**, *135*, 11481−11484. (d) Zhang, C.; Jiao, N. Dioxygen activation under ambient conditions: Cu-catalyzed oxidative amidation−diketonization of terminal alkynes leading to *α*-ketoamides. *J. Am. Chem. Soc.* **2010**, *132*, 28−29. (e) Hu, Y.; Yi, R.; Wang, C.; Xin, X.; Wu, F.; Wan, B. From propargylamides to oxazole derivatives: NIS-mediated cyclization and further oxidation by dioxygen. *J. Org. Chem.* **2014**, *79*, 3052−3059.

(18) For selected examples, see: (a) Zhu, C.; Yi, M.; Wei, D.; Chen, X.; Wu, Y.; Cui, X. Copper-catalyzed direct amination of quinoline *N*-oxides via C−H bond activation under mild conditions. *Org. Lett.* **2014**, *16*, 1840−1843. (b) Huang, H.; Ji, X.; Tang, X.; Zhang, M.; Li, X.; Jiang, H. Conversion of pyridine to imidazo[1,2-a]pyridines by copper-catalyzed aerobic dehydrogenative cyclization with oxime esters. *Org. Lett.* **2013**, *15*, 6254−6257. (c) Lu, J.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. Copper-catalyzed aerobic oxidative intramolecular alkene C−H amination leading to N-heterocycles. *Org. Lett.* **2011**, *13*, 3694−3697. (d) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. Copper-catalyzed sequential Ullmann N-arylation and aerobic oxidative C−H amination: A convenient route to indolo[1,2-c]quinazoline derivatives. *Org. Lett.* **2012**, *14*, 3894−3897. (e) Oda, Y.; Hirano, K.; Satoh, T.; Miura, M. Synthesis of N-azolylindoles by copper-catalyzed C−H/N−H coupling-annulation sequence of *o*-alkynylanilines. *Org. Lett.* **2012**, *14*, 664−667. (f) Selvaraju, M.; Sun, C. One-pot synthesis of triazoloquinazolinones via copper-catalyzed tandem click and intramolecular C−H amidation. *Adv. Synth. Catal.* **2014**, *356*, 1329−1336. (g) Mitsuda, S.; Fujiwara, T.; Kimigafukuro, K.; Monguchi, D.; Mori, A. Copper-catalyzed oxidative C−H, N−H coupling of azoles and thiophenes. *Tetrahedron.* **2012**, *68*, 3585−3590. (h) Wang, Q.; Schreiber, S. L. Copper-mediated amidation of heterocyclic and aromatic C−H bonds. *Org. Lett.* **2009**, *11*, 5178. (i) Xu, H.; Fu, H. Copper-catalyzed one-pot synthesis of imidazo/benzoimidazoquinazolinones by sequential Ullmann-type coupling and intramolecular C−H amidation. *Chem.—Eur. J.* **2012**, *18*, 1180−1186. (j) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. Direct amination of azoles via catalytic C−H, N−H coupling. *Org. Lett.* **2009**, *11*, 1607.

(19) Ma, D.; Cai, Q. Copper/Amino Acid Catalyzed Cross-Couplings of Aryl and Vinyl Halides with Nucleophiles. *Acc. Chem. Res.* **2008**, *41*, 1450−1460.

(20) Three representative examples are shown as follows: (**3**{*1,1*}). Eluent: Petroleum ether/ethyl acetate (3:1). White solid, 77 mg, 89% yield, mp 201−203 °C (petroleum ether/ethyl acetate = 4:1, R_f = 0.2). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 8.47 (d, 1H, J = 80. Hz), 8.24 (d, 1H, J = 8.0 Hz), 8.17 (dd, 1H, J = 8.0 Hz), 8.05 (dt, 1H, J = 8.0 Hz), 7.71 (t, 1H, J = 8.0 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.60−7.52 (m, 5H), 7.47−7.39 (m, 2H). ^{13}C NMR (DMSO-*d*6, 200 MHz, ppm): δ 146.6, 141.1, 135.7, 133.4, 132.5, 130.6, 129.9, 129.7, 129.1, 126.5, 126.1. 124.4, 123.7, 123.4, 119.5, 118.6, 112.6. HRMS calcd for $C_{19}H_{13}N_3O_2S$ $(M + H)^+$ 348.0807; found, 348.0816.. (**3**{*2,1*}). Eluent: Petroleum ether/ethyl acetate (2:1). White solid, 85 mg, 94% yield, mp 195−197 °C (petroleum ether/ethyl acetate = 2:1, R_f = 0.2). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 8.46 (d, 1H, J = 8.0 Hz), 8.20 (dd, 1H, J = 8.0 Hz), 8.17 (dd, 1H, J = 8.0 Hz), 8.05 (dt, 1H, J = 8.0 Hz), 7.72−7.64 (m, 2H),7.44−7.36 (m, 6H), 2.40 (s, 3H). ^{13}C NMR (DMSO-*d*6, 200 MHz, ppm): δ 147.2, 141.7, 140.1, 136.1, 132.9, 131.1, 131.1, 131.0, 130.8, 129.4, 126.9, 126.6, 124.8, 124.3, 123.9, 119.8, 119.0, 113.2, 21.2. HRMS calcd for $C_{20}H_{15}N_3O_2S$ $(M + H)^+$, 362.0963; found, 362.0916.. (**3**{*12,1*}). Eluent: Petroleum ether/ethyl acetate (3:1). Pale yellow solid, 70 mg, 79% yield, mp 94−95 °C (petroleum ether/ethyl acetate = 4:1, R_f = 0.4). ^{1}H NMR (DMSO-d_6, 400 MHz, ppm): δ 8.38 (d, 1H, J = 8.0 Hz), 8.19−8.14 (m, 2H), 8.00 (d, 1H, J = 8.0 Hz), 7.76 (t, 1H, J = 8.0 Hz), 7.67 (t, 1H, J = 8.0 Hz), 7.42 (t, 1H, J = 8.0 Hz), 4.10 (t, 3H, J = 8.0 Hz), 1.34−1.22 (m, 8H), 0.81 (t, 3H, J = 8.0 Hz). ^{13}C NMR (DMSO-d_6, 200 MHz, ppm): δ 146.5, 141.8, 135.8, 132.7, 131.0, 126.8, 126.3, 124.8, 123.6, 119.6,

DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119

118.5, 113.2, 45.3, 31.0, 28.5, 26.0, 22.4, 14.2. HRMS calc. for $C_{16}H_{15}N_3O_2S$ $(M + H)^+$, 355.1354; found, 355. 1354..

(21) (a) Xie, X.; Chen, Y.; Ma, D. Enantioselective arylation of 2-methylacetoacetates catalyzed by CuI/*trans*-4-hydroxy-l-proline at low reaction temperatures. *J. Am. Chem. Soc.* **2006**, *128*, 16050−16051. (b) Cai, Q.; Zou, B.; Ma, D. Mild Ullmann-type biaryl ether formation reaction by combination of ortho-substituent and ligand effects. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276−1279.

DOI: 10.1021/co500125n
ACS Comb. Sci. 2015, 17, 113−119