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Palladium-Catalyzed Synthesis of 2-Substituted Benzothiazoles via a C−H Functionalization/Intramolecular C−S Bond Formation Process

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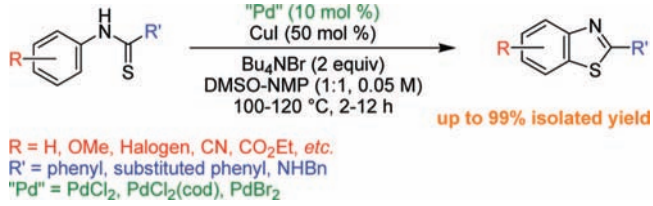
ABSTRACT



Catalytic synthesis of 2-substituted benzothiazoles from thiobenzanilides was achieved in the presence of a palladium catalyst through C−H functionalization/C−S bond formation. This method features the use of a novel catalytic system consisting of 10 mol % of Pd(II), 50 mol % of Cu(I), and 2 equiv of Bu_4NBr that produced variously substituted benzothiazoles in high yields with good functional group tolerance.

Transition metal-catalyzed C−H functionalization has emerged, over the past decade, as a highly attractive and powerful strategy to construct complex molecules.[1] Various catalytic systems based on rhodium,[2] ruthenium,[3] and palladium[4] have been developed to effect C−C and C−heteroatom (nitrogen and oxygen) bond formation. Copper has also been used to catalyze this process recently.[5] In this area, intermolecular C−H functionalization has been extensively studied, while much less attention has been paid to intramolecular functionalization, which would provide more facile access to a range of carbo- and heterocycles.[2a,e,3b,4c,bb,6−8] Our group has already developed an efficient method for indazole synthesis through a palladium-catalyzed C−H functionalization/intramolecular amination sequence.[6] Recently, Buchwald reported a new approach to benzimidazoles making use of a copper-catalyzed intramolecular C−H amination reaction.[7] During the preparation of this manuscript, Nagasawa reported the synthesis of 2-arylbenzoxazoles via intramolecular C−O oxidative coupling in the presence of 20 mol % of $Cu(OTf)_2$.[8] In this communication, we wish to describe a novel Pd-catalyzed cyclization of thiobenzanilides through a C−H functionalization/C−S bond formation process, leading to a range of substituted benzothiazoles. Yields were generally good to high in this cyclization and good functional group tolerance (e.g., ethoxycarbonyl, cyano, etc.) was

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(2) For selected recent examples, see (C−N bond formation): (a) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056. (b) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343. (c) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* 2007, *129*, 562 (C−C bond formation): (d) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (e) Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6316.

(3) For selected recent examples, see (C−N bond formation): (a) Lin, X.; Che, C.-M.; Phillips, D. L. *J. Org. Chem.* 2008, *73*, 529 (C−C bond formation): (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (c) Foley, N. A.; Gunnoe, T. B.; Cundari, T. R.; Boyle, P. D.; Petersen, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 726. (d) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858.

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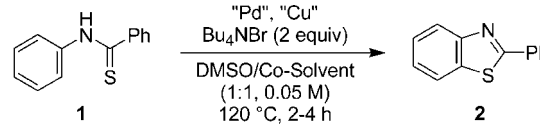
observed in our catalyst system. Indeed, the method developed here represents a rare example of C−S bond formation through transition-metal-catalyzed C−H functionalization.[9]

Benzothiazoles are a considerably important class of heterocycles in the medicinal area due to their broad range of biological activities.[10] Oxidative cyclization of thiobenzanilides using various oxidants, including Jacobson's and Hugershoff's methods, has been among the most widely used routes to benzothiazoles.[11,12] However, low functional group tolerance is a major drawback of these methods as substituents such as the alkoxycarbonyl group or the cyano group seem difficult to retain intact in Jacobson's synthesis.[12c] Using stoichiometric or excess amounts of toxic reagents, such as bromine[12a] or metals,[12c,e] may also have disadvantages. Pd- or Cu-catalyzed cyclization of 2-halophenylthiobenzamides provide another access to benzothiazoles.[13] It is necessary to prefunctionalize starting materials in this reaction, which significantly limits the utility and applicability of this approach.

We began our study by examining the reaction of thiobenzanilide **1** to 2-phenylbenzothiazole **2** in DMSO to obtain the optimal reaction conditions (Table 1). During an initial screening of the palladium/reoxidant combination, we found that the addition of Bu_4NBr considerably enhanced this process (Table 1, entry 1 vs entry 2). Encouraged by this result, we further examined this reaction using $PdCl_2$ as a palladium source. CuI proved to be best among an array of copper salts tested (Table 1, entries 3−9). Interestingly, the catalytic activity was maintained when the amount of CuI was decreased to 50 mol % (Table 1, entries 10 and 11). The cosolvent effect was also investigated in the

Table 1. Effect of Reaction Parameters



1 2

entry	"Pd" (mol %)	"Cu" (mol %)	Bu_4NBr	cosolvent	yield[a] (%)
1[b]	$Pd(OAc)_2$ (30)	$Cu(OAc)_2$ (100)	−	−	16
2	$Pd(OAc)_2$ (30)	$Cu(OAc)_2$ (100)	+	−	49
3	$PdCl_2$ (30)	$Cu(OAc)_2$ (100)	+	−	56
4	$PdCl_2$ (30)	$Cu(OTf)_2$ (100)	+	−	12
5	$PdCl_2$ (30)	$Cu(acac)_2$ (100)	+	−	47
6	$PdCl_2$ (30)	CuF_2 (100)	+	−	31
7	$PdCl_2$ (30)	$CuCl_2$ (100)	+	−	13
8	$PdCl_2$ (30)	$CuBr_2$ (100)	+	−	8
9	$PdCl_2$ (20)	CuI (100)	+	−	65
10	$PdCl_2$ (20)	CuI (50)	+	−	65
11	$PdCl_2$ (10)	CuI (50)	+	−	42
12	$PdCl_2$ (10)	CuI (50)	+	dioxane	31
13	$PdCl_2$ (10)	CuI (50)	+	*o*-xylene	45
14	$PdCl_2$ (10)	CuI (50)	+	2-BuOH	43
15	$PdCl_2$ (10)	CuI (50)	+	DMF	48
16	$PdCl_2$ (10)	CuI (50)	+	NMP	74
17	$PdCl_2$(cod) (10)	CuI (50)	+	NMP	79
18	$PdBr_2$ (10)	CuI (50)	+	NMP	79
19	$PdCl_2$ (5)	CuI (50)	+	NMP	53
20	$PdCl_2$ (10)	CuI (100)	−	NMP	<2
21	$PdCl_2$ (10)	0	+	NMP	34
22	$PdCl_2$ (10)	0	−	NMP	3
23	0	CuI (50)	+	NMP	0 (84)[c]
24	0	CuI (50)	−	NMP	0
25	0	0	+	NMP	0 (quant)[c]

[a] Yield of isolated product from reaction on a 0.14−0.29 mmol scale. [b] 39 h. [c] Yield of recovered starting material in parentheses.

(4) For selected recent examples, see (C−C bond formation): (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (c) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636. (d) Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304. (e) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (f) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (g) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900. (h) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (i) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (j) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (k) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (l) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (m) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (n) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (o) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333. (p) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (q) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (r) Shabashov, D.; Daugulis, O. *Org. Lett.* **2006**, *8*, 4947. (s) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (t) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (u) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211. (v) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (w) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (x) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (y) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W., Gevorgyan, V. *Org. Lett.* 2004, *6*, 1159 (C−halogen bond formation): (z) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523(C−N bond formation): (aa) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (bb) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.

(5) (C−heteroatom bond formation): (a) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790 (C−C bond formation). (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

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(9) Very recently, we reported the Pd(II)-catalyzed one-pot conversion of thioenols into benzo[*b*]thiophenes via the formation of disulfides, see: Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, DOI: 10.1039/<B811362A>.

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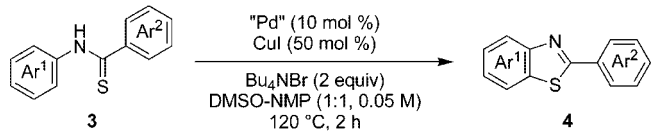
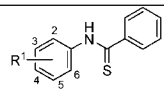
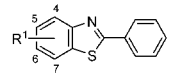
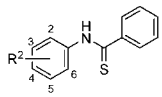
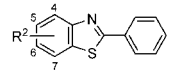
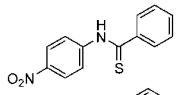
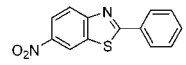
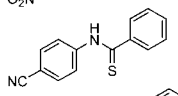
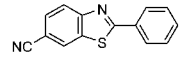
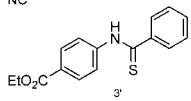
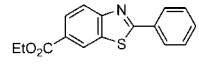
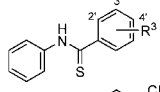
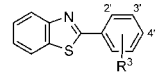
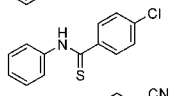
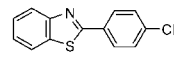
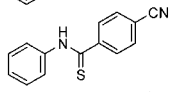
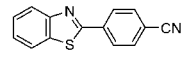
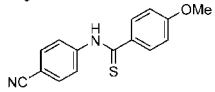
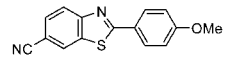
(12) For selected recent examples, see: (a) Thiel, O. R.; Bernard, C.; King, T.; Dilmeghani-Seran, M.; Bostick, T.; Larsen, R. D.; Faul, M. M. *J. Org. Chem.* **2008**, *73*, 3508. (b) Bose, D. S.; Idrees, M.; Srikanth, B. *Synthesis* **2007**, 819. (c) Wang, M.; Gao, M.; Mock, B. H.; Miller, K. D.; Sledge, G. W.; Hutchins, G. D.; Zheng, Q.-H. *Bioorg. Med. Chem.* **2006**, *14*, 8599. (d) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (e) Mu, X.-J.; Zou, J.-P.; Zeng, R.-S.; Wu, J.-C. *Tetrahedron Lett.* **2005**, *46*, 4345.

(13) (a) Vera, M. D.; Pelletier, J. C. *J. Comb. Chem.* **2007**, *9*, 569. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446. (d) Benedí, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073.

Table 2. Synthesis of Variously Substituted 2-Arylbenzothiazoles



3 **4**

entry	substrate	3	product	4	yield (%, **A** / **B** / **C**)[a,b]
1		**3a** (R^1 = 4-OMe)		**4a** (R^1 = 6-OMe)	65 / 57 / 62
2		**3b** (R^1 = 3-OMe)		**4b** (R^1 = 5-OMe)	81 / 82 / 83
3		**3c** (R^1 = 2-OMe)		**4c** (R^1 = 4-OMe)	34 / 24 / 23[c]
4		**3d** (R^2 = 4-Cl)		**4d** (R^2 = 6-Cl)	74 / 74 / 71
5		**3e** (R^2 = 4-Br)		**4e** (R^2 = 6-Br)	>99 / 99 / 71
6		**3f** (R^2 = 3-Br)		**4f** (R^2 = 5-Br)	53 / 65 / 34
7		**3g** (R^2 = 4-I)		**4g** (R^2 = 6-I)[d]	73 / 75 / 72
8[e]		**3h** (R^2 = 2-F)		**4h** (R^2 = 4-F)[d]	75 / 73 / 63
9		**3i**		**4i**	83 / 90 / 82
10		**3j**		**4j**	78 / 81 / 67
11		**3k**		**4k**	78 / 76 / 73
12		**3l** (R^3 = 4'-OMe)		**4l** (R^3 = 4'-OMe)	56 / 45 / 44
13		**3m** (R^3 = 3'-OMe)		**4m** (R^3 = 3'-OMe)	61 / 56 / 63
14[e]		**3n**		**4n**	71 / 62 / 73
15[e]		**3o**		**4o**	71 / 75 / 62
16		**3p**		**4p**	75 / 65 / 71

[a] Yield of isolated product from reaction on a 0.14 mmol scale. [b] **A**: with $PdCl_2$, **B**: with $PdCl_2$(cod), **C**: with $PdBr_2$. [c] Formation of the corresponding benzanilide was observed (58−76%). [d] Obtained as a mixture of the desired product and its dehalogenated compound (up to 11%). Yield was determined by ^{1}H NMR spectrum. [e] 6 h.

presence of 10 mol % of $PdCl_2$ and 50 mol % of CuI (Table 1, entries 12−16). When NMP was used as a cosolvent (1:1 ratio) the process was greatly accelerated; the desired cyclized product was obtained in 74% yield using these conditions (Table 1, entry 16). $PdCl_2$(cod) and $PdBr_2$ were found to have comparable catalytic activity (Table 1, entries 17 and 18). The combination of $PdCl_2$ and CuI in the *absence* of Bu_4NBr had no catalytic activity at all (entry 20). Essentially, no satisfactory results were obtained when only a palladium or copper salt was used in this cyclization (Table 1, entries 21−24).[14]

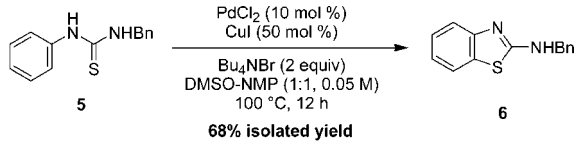
With the optimized reaction conditions identified, the scope of this method was investigated using variously substituted thiobenzanilides **3** (Table 2), which were readily prepared from condensation of the corresponding anilines and benzoyl chlorides followed by thionation.[14] As indicated in Table 2, a range of 2-arylbenzothiazoles with both electron-donating and electron-withdrawing groups were produced in high yields using the optimal reaction conditions. A particularly appealing feature of this system is its functional group compatibility; the alkoxycarbonyl group (entry 11), the cyano group (entries 10 and 15), and the halogen atoms including iodine (entries 4−8 and 14) are well tolerated during the reaction. The reactions of substrates which possess a substituent at the 3-position (**3b** and **3f**) occurred regioselectively at the less sterically hindered 6-position; the corresponding benzothiazoles (**4b** and **4f**) were obtained exclusively and no regioisomers were observed (entries 2 and 6).

The developed method can be successfully extended to the synthesis of 2-aminobenzothiazole. Substrate **5** thus underwent the Pd-catalyzed cyclization to give the cyclized product **6** in 68% yield (Scheme 1).

Although extensive studies on reaction mechanism have not yet been carried out, a mechanism analogous to those proposed for similar palladium-catalyzed processes might be

(14) For synthetic procedures in preparation of starting materials, analytical data, and detailed results of screenings, see the Supporting Information.

Scheme 1. Synthesis of 2-Aminobenzothiazole **6**



applicable to this cyclization.[4aa,bb,6] It is conceivable that Bu_4NBr, along with CuI, might be involved in the reoxidation step of palladium(0) in the catalytic cycle.

In summary, we have achieved the catalytic C−H functionalization/C−S bond formation sequence employing 10 mol % of palladium(II) catalysts in the synthesis of 2-substituted benzothiazoles. The use of Bu_4NBr greatly enhanced this transformation, which enabled this process to be performed efficiently and quickly. In addition to the generality with respect to the substrate scope, facile accessibility to the starting materials is also highly appealing. This versatile synthetic method is expected to find valuable application in various areas, especially in medicinal chemistry. Our results clearly demonstrate the potential of the catalytic approach with palladium in the synthesis of sulfur-based heterocycles. Further investigations to understand the precise reaction mechanism as well as to apply this system to the construction of other sulfur-based heterocycles are underway.

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Supporting Information Available: Detailed experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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