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Heterocycle Formation via Palladium-Catalyzed Intramolecular Oxidative C−H Bond Functionalization: An Efficient Strategy for the Synthesis of 2-Aminobenzothiazoles

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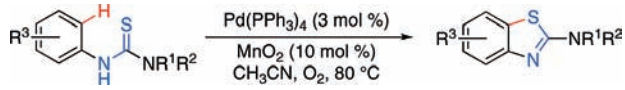
ABSTRACT



***N*-Arylthioureas are converted to 2-aminobenzothiazoles via intramolecular C−S bond formation/C−H functionalization utilizing an unusual cocatalytic $Pd(PPh_3)_4/MnO_2$ system under an oxygen atmosphere at 80 °C. This method eliminates the need for an *ortho*-halo substituted precursor, instead achieving direct functionalization of the *ortho*-aryl C−H bond. Mechanistic observations, including a large intramolecular primary kinetic isotope effect of 5.9, reveal a reaction pathway inconsistent with an electrophilic palladation mechanism.**

The importance of transition metal-catalyzed C−H "activation" chemistry has grown rapidly in recent years,[1] with particular interest being afforded to palladium mediated/catalyzed chelate-directed functionalization reactions.[2] While most examples reported have been intermolecular functionalizations, only recently, following Buchwald's report of Pd(II)/Cu(II) mediated carbazole formation,[3] has attention turned to the use of these oxidative functionalization reactions for the formation of heterocyclic ring systems *via* intramolecular cyclizations.[4] Several groups including our own have explored Pd and Cu catalyzed reactions of *ortho*-halo-substituted aromatics for the formation of a variety of benz-fused heterocycles.[5] For example, thiourea **1** undergoes

(1) For selected recent reviews on transition metal-catalyzed C-H functionalizations, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth.Catal.* **2003**, *345*, 1077–1101. (b) Goj, L. A.; Gunnoe, T. B. *Curr. Org. Chem.* **2005**, *9*, 671–685. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463. (d) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041–4047. (e) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382–3388. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (h) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41.

(2) For selected recent examples using Pd catalysis, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (c) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049. (d) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416–7417. (e) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528–2529. (f) Wang, J.-R.; Yang, C.-T.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 5449–5453. (g) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924–2935. (h) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (i) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996–8000. (j) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904–11905. (k) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207–2210. (l) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

(3) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560–14561.

(4) (a) Sridharan, V.; Martín, M. A.; Menéndez, C. M. *Synlett* **2006**, *15*, 2375–2378. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137–3139. (c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186.

(5) (a) Takagi, K. *Chem. Lett.* **1986**, 265–266. (b) Brain, C. T.; Bunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893–1895. (c) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133–136. (d) Benedi, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073–6077. (e) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446–447. (f) Orain, D.; Blumstein, A.-C.; Tasdelen, E.; Haessig, S. *Synlett* **2008**, 2433–2436.

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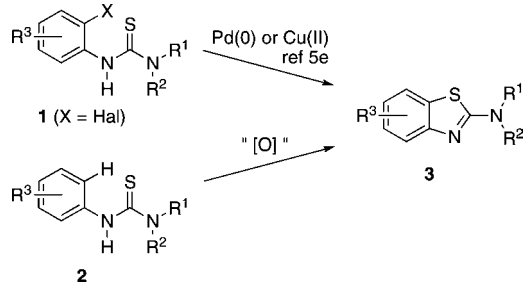
intramolecular cross-coupling to give 2-aminobenzothiazoles[6] **3** (Figure 1).[5c] The requirement for an *ortho*-halo substituted precursor (such as **1**) would be eliminated if a direct C−H bond functionalization/cyclization could be achieved, thus opening up a much wider range of more readily accessible precursors for benz-fused heterocycle synthesis.[7] Herein, we report the successful realization of this strategy using palladium catalysis under oxidative conditions,[8,9] for the conversion of *N*-arylthiourea substrates **2** into **3** (Scheme 1).[10]

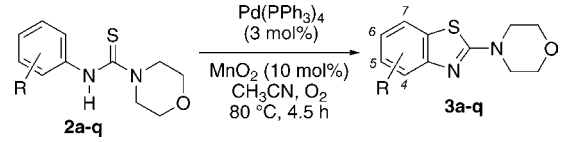
Scheme 1. Metal Catalyzed Cyclization Strategies for 2-Aminobenzothiazole Formation



Initial optimization studies using model substrate **2a** (NR^1R^2 = morpholino and R^3 = H) under catalytic oxidative conditions were not encouraging. However, overnight screening reactions of stoichiometric Pd complexes in acetonitrile under a N_2 atmosphere, at 75 °C, revealed that whereas Pd(II) complexes[11] afforded product **3a** in low 12−31% yields, use of zerovalent $Pd(PPh_3)_4$ led to an improved 47% yield. This result was unexpected as most oxidative functionalizations make use of Pd(II) catalysts, typically $Pd(OAc)_2$. Reaction of **2a** under an O_2 atmosphere using 10 mol % $Pd(PPh_3)_4$ in MeCN solvent at 80 °C gave a 40% yield of **3a** after 2 h.[12] Introduction of the catalytic co-oxidant $Cu(OAc)_2 \cdot H_2O$ (10 mol %) under otherwise identical conditions further improved the yield to 72% after 2 h. Other terminal oxidants such as *p*-benzoquinone, NMO, and DMSO, were less efficient (9−53% yield), while reaction in the absence of a terminal oxidant afforded just a 6% yield of **3a**. Evidence of substrate acetoxylation, however, seen with the $Cu(OAc)_2$ co-oxidant, led us to investigate the use of alternative co-oxidants. A broad screen of catalytic co-oxidants revealed both $Cu(acac)_2$ and CuCl salts to be effective, giving 72 and 59% yields, respectively. Activated MnO_2 was unexpectedly the most efficient co-oxidant giving a quantitative yield of **3a** at half the loading of $Pd(PPh_3)_4$, and with a higher rate of conversion; use of MnO_2 (5 mol %) alone did not result in product formation. These results highlight the importance of the combination of $Pd(PPh_3)_4$ and activated MnO_2 for these oxidative cyclizations.

The optimized reaction conditions were evaluated for a range of substituted precursors **2** (Table 1). *Para*-substituted aryl thioureas worked well; however, the more electron-rich *p*-MeO-substituted precursor **2e** reacted in lower yield (Table 1, entries 2−5). *Meta*-substituted substrates cyclized chemoselectively to give the 5-substituted products **3g**−**3i** exclusively, except for the *m*-F substrate which gave a 9:1 mixture of 5-substituted:7-substituted products **3f** (Table 1, entries 6−9). Incorporation of two *meta*-substituents resulted in very poor conversions for **2j** and **2k**, and only modest conversion was achieved for **2l** (Table 1, entries 10−12). While the majority

Table 1. Effect of Aryl Substituents on 2-Aminobenzothiazole Formation



entry	substrate	R	convn (%)[a]	yield (%)[b]
1	**2a**	H	≥99	89
2	**2b**	*p*-F	≥99	90
3	**2c**	*p*-NO_2	≥99	92
4	**2d**	*p*-Me	≥99	87
5	**2e**	*p*-OMe	70	66[c]
6	**2f**	*m*-F	90	84[d]
7	**2g**	*m*-Cl	≥99	84
8	**2h**	*m*-Me	≥99	93
9	**2i**	*m*-OMe	≥99	83
10	**2j**	*m*,*m*-Me	≤1	0
11	**2k**	*m*,*m*,*p*-OMe	3	3
12	**2l**	*m*,*m*-F	60	35[e]
13	**2m**	*o*-Et	≥99	87
14	**2n**	*o*,*m*- 	≥99	96
15	**2o**	*o*-F	≥99	89
16	**2p**	*o*-Cl	~80	74[f]
17	**2q**	*o*-Br	~20	0[g]

[a] Conversion determined by ^{1}H NMR spectroscopy. [b] Yields after silica gel column chromatography. [c] 22% starting material recovered; complete conversion and 88% yield are obtained after a reaction time of 24 h. [d] Ratio of 9:1 5-F/7-F products. [e] 39% starting material recovered. [f] 16% starting material recovered and 3% of **3a**. [g] 68% starting material recovered and 11% of **3a**.

(6) A class of heterocycles having significant pharmaceutical importance. For examples, seeFrentizole (immunosuppressant): (a) Paget, C. J.; Kisner, K.; Stone, R. L.; DeLong, D. C. *J. Med. Chem.* **1969**, *12*, 1016–1018. Zolantidine (centrally acting H_2-receptor histamine antagonist): (b) Young, R. C.; Mitchell, R. C.; Brown, T. H.; Ganellin, C. R.; Griffiths, R.; Jones, M.; Rana, K. K.; Saunders, D.; Smith, I. R.; Sore, N. E.; Wilks, T. J. *J. Med. Chem.* **1988**, *31*, 656–671.

(7) For a general overview of synthetic methods to benzthiazoles, see: (a) Ulrich, H. in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Schaumann, E., Ed.; Thieme: Stuttgart, 2001; Vol. 11, pp 835−912.

(8) This work was presented in part at 234th American Chemical Society National Meeting, Boston, MA, August 19−23, **2007**. Abstract #325.

(9) During the course of our studies two examples on copper catalyzed benzimidazole and benzoxazole formation via C−H functionalization were reported, see: (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934. (b) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411–6413.

(10) The precursors **2** are readily synthesized through the facile reaction of commercially available phenylisothiocyantes with secondary amines in less than 10 min, in typically quantitative yields.

(11) Pd(II) sources tested: $PdCl_2(CH_3CN)_2$, $Pd(OAc)_2$, and $PdCl_2(1,5\text{-}C_8H_{12})$.

(12) This and subsequent optimization reactions were monitored *via* HPLC using a naphthalene internal standard as a reference.

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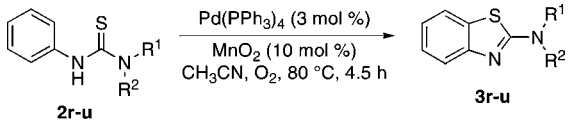
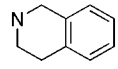
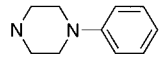
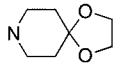
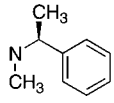
of *ortho*-substituted precursors effectively underwent reaction (Table 1, entries 13−15), *o*-chloro and -bromo substituted compounds (Table 1, entries 16−17) led to lower conversions and competitive cyclization to the dehalogenated cyclized product **3a**. The reaction of other trisubstituted aminophenylthioureas generally proceeded well, giving excellent conversions and high yields (Table 2).

Table 2. C−S Bond Forming Cyclization Reaction Substrate Scope



2r-u **3r-u**

entry	substrate	NR^1R^2	convn (%)[a]	yield (%)[b]
1	**2r**		100	93
2	**2s**		100	93
3	**2t**		100	90
4	**2u**		100	90

[a] Conversion determined by ^{1}H NMR spectroscopy. [b] Yields after silica gel column chromatography.

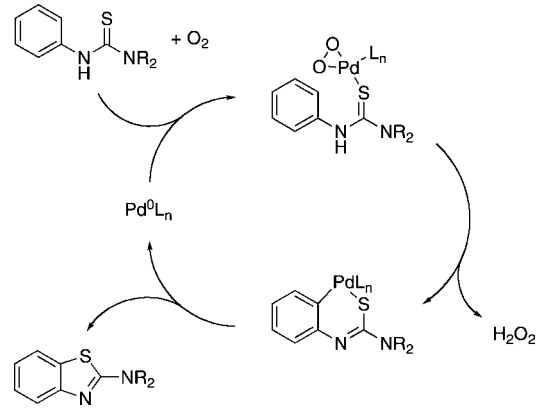
A catalyst system comprising $Pd_2(dba)_3$ (1 mol %), PPh_3 (8 mol %) and MnO_2 (10 mol %) is also effective giving **3a** in quantitative yield after 4 h under an O_2 atmosphere. Lowering the amount of PPh_3 ligand led to lowered reactivity and yields of **3a**, with no product being obtained in the absence of the ligand. *In situ* catalyst formation by addition of free PPh_3 (4 or 10 equiv) to $Pd(OAc)_2$ under an O_2 atmosphere was also successful giving yields of 34 and 81%, respectively. These results demonstrate the importance of using a Pd(0)/phosphine based catalyst system.[13,14] The utility of similar systems have been reported in the oxidative homocoupling of arylboronic esters[15] and acids,[16] as well as in the oxidation of allylic alcohols to α,β-unsaturated carbonyl compounds.[17]

As with many oxidative C−H functionalization reactions, a full mechanistic understanding of the reaction has yet to be established, however, some observations can be made. Addition of a free-radical trap (galvinoxyl, 30 mol %) was found to have no effect on the reaction, suggesting that a radical pathway does not operate.[18] Competition experiments reveal that substrates bearing electron-withdrawing groups at the *para*-position (e.g., *p*-CN or *p*-NO_2) undergo cyclization more rapidly than **2a**, whereas substrate **2e** bearing an electron donating *p*-OMe group undergoes cyclization more slowly. The effects are similar, although less pronounced, with *meta*-substituted examples. The higher reactivity of the more electron deficient substrates is inconsistent with an electrophilic palladation mechanism.

Treatment of mono-*ortho*-deuterium enriched *N*-phenylbenzothiourea with $Pd(PPh_3)_4$ (10 mol %) and MnO_2 (20 mol %) in CH_3CN for 5.5 h under an O_2 atmosphere at 80 °C resulted in complete conversion to the cyclized product 2-phenylbenzothiazole. This transformation occurred with a high intramolecular primary KIE of 5.9, showing preferential functionalization of the C−H bond over a C−D bond. An intramolecular primary KIE of 5.9 is similar to isotope effects observed in aromatic palladation reactions and intramolecular palladium-catalyzed cyclizations.[19−23] This comparison provides further support to suggest that an electrophilic palladation mechanism does not operate, as such reactions typically do not exhibit primary KIEs because aryl deprotonation is fast relative to the formation of an arenium σ-complex.[24]

The chemoselectivity of cyclization of substrates **2f**−**2i** and the poor reactivity of **2j** and **2k** suggest that the reaction

Scheme 2. Potential Mechanistic Overview of Aminobenzothiazole Formation



(13) Screening of a variety of other phosphines under the same conditions led to lowered yields of **3a**: PCy_3, P(*o*-tol)$_3$, and P(2-fur)$_3$ ranging from 3−5%; Buchwald ligands DavePhos, JohnPhos, and Ph XPhos from 1−12%; and bidentate ligands DPPB, DPPF, and XantPhos from 17−32%.

(14) The superiority of PPh_3 as a ligand may reflect its greater stability towards oxidation, as ligand loss through oxidation results in termination of the catalytic cycle. See Iyer, S.; Kulkarni, G. M.; Ramesh, C. *Tetrahedron* **2004**, *60*, 2163–2172.

(15) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541–1544.

(16) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2000**, *42*, 4087–4089.

(17) Gomez-Bengoa, E.; Noheda, P.; Echavarran, M. A. *Tetrahedron Lett.* **1994**, *35*, 7097–7098.

(18) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331.

(19) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636–5637 (k_H/k_D = 3.5).

(20) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886. (k_H/k_D = 5.0−6.7).

(21) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635 (k_H/k_D = 3.0−7.0).

(22) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587 (k_H/k_D = 3).

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is very sensitive to steric effects at the *ortho*-position adjacent to the C−H bond undergoing functionalization. In combination these observations may suggest that a σ-bond metathesis mechanism occurs, wherein an anionic peroxo/peroxide-Pd-bound ligand aids in proton abstraction (Scheme 2).

While the role of MnO_2 remains unclear, it may serve as a catalyst for hydrogen peroxide decomposition. The heterogeneous surface of may also aid in the generation of a peroxo-Pd(II) species or enhance catalyst stability. Interestingly, another heterogeneous additive, 4 Å molecular sieves,[25] also had a beneficial effect on overall reaction conversions (in the absence of MnO_2). However, much larger amounts of 4 Å molecular sieves were required relative to MnO_2, rendering this approach less practical.

In summary, we have established a Pd/Mn based catalyst system for 2-aminobenzothiazole formation via an oxidative C−H functionalization. Further studies on related systems and the broader use of mixed Pd/Mn based oxidative catalysis are currently underway.

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

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(23) Shue, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 7116–7117 ($k_H/k_D = 5$).
(24) Campeau, C.-L.; Fagnou, K. *Chem. Commun.* **2006**, 1253–1264.

(25) Several groups have demonstrated the beneficial effect of molecular sieves on aerobic palladium(II) catalyzed oxidation of alcohols. See for example:(a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755. (b) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343–3352. (c) Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861–1868.

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