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General and practical synthesis of benzothiazoles*,**

Toshiaki Mase‡ and Takahiro Itoh

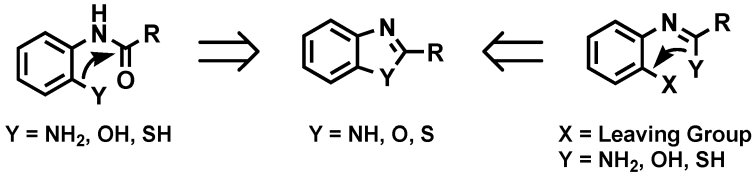
Process Research, Preclinical Development, Banyu Pharmaceutical Co., Ltd. Okubo 3, Tsukuba, Ibaraki 300-2611, Japan

Abstract: The carbon–sulfur bond formation of aryl bromides and triflates catalyzed by a new catalyst system, $Pd_2(dba)_3$/xantphos, has been demonstrated. Based on this finding, a novel and practical synthesis of benzothiazoles has been developed. This new methodology allows for the assembly of a wide range of benzothiazoles.

Keywords: palladium-catalyzed coupling; aryl bromides; aryl triflates; thiol surrogates; benzothiazole; xantphos.

INTRODUCTION

Benzazoles are an extremely important class of compounds that occur widely as biologically active natural products, as well as marketed drugs or drug candidates [1]. Accordingly, the development of efficient and general synthetic methodology for benzazoles is a meaningful research challenge having great potential for practical applications in the pharmaceutical industry. Benzazoles have two heteroatoms attached at the ortho position on the benzene ring. Since one nitrogen atom is common for all three benzazoles, two carbon-hetero atom (C–Y) bonds can be cleaved retrosynthetically, generating the right- and the left-hand approaches, respectively, as shown in Scheme 1. In relation to these two approaches, there is no doubt that Buchwald/Hartwig-type cross-coupling would be one of the most powerful tools to attach heteroatom bonds to aromatic rings.



Scheme 1 Cross-coupling approaches to benzazoles.

The right-hand approach includes an intramolecular cyclization of anilides and its derivatives having a leaving group at the *o*-position promoted by a transition-metal catalyst. Batey and coworkers recently demonstrated this methodology using Cu or Pd catalyst [2]. This method is particularly efficient

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‡Corresponding author

for the synthesis of oxazolines (Y=OH) because various amide compounds, which are readily available in general, can directly be converted into the desired benzoxazoles. However, for benzimidazoles or thiazoles, the required amidines/guanidines or thiocarbonyl precursors are sometimes difficult to prepare, and available methodology may be complicated by problems arising from incompatibility of functional groups. For example, functional groups such as ketone, esters, and amides are often incompatible with methods commonly used to prepare thioanilides [2a,3].

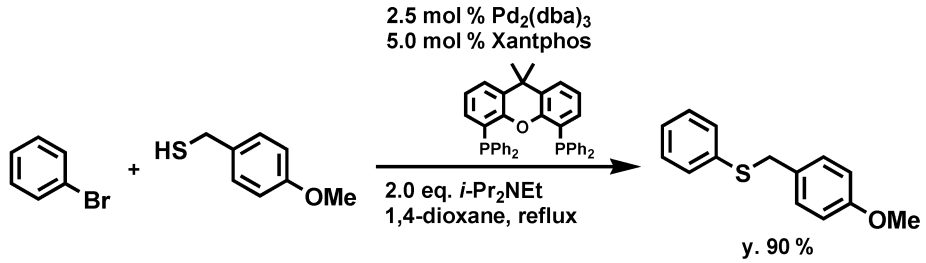
The left-hand approach includes a usual intramolecular cyclization via introduction of unprotected heteroatoms by a typical aryl-heteroatom cross-coupling protocol [4]. Very recently, Ma and coworkers have demonstrated this methodology using a Cu catalyst with several primary amines, which provides access to 1,2-disubstituted benzimidazoles [5]. Their work stimulated us to publish our research on the synthesis of benzothiazoles via Pd-catalyzed cross-coupling with a H_2S surrogate.

In order to synthesize benzothiazoles or benzimidazoles, unprotected SH or NH_2 groups are necessary. For aromatic amination, numerous reports including coupling with NH_3 or its surrogates have already been reported [6]. Indeed, in 2001, Lang and coworkers reported Cu-catalyzed coupling with atom-efficient ammonia, leading to aniline derivatives [7]. Several groups also reported excellent ammonia surrogates like hexamethyldisilazide for the coupling reactions [8]. In addition, recently Pd-catalyzed coupling reactions with NH_3 or $LiNH_2$ were reported by Hartwig [9]. The direct synthesis of phenol via Pd-catalyzed reaction with KOH has also been demonstrated by Buchwald [10]. In contrast, however, the sulfur variation of this chemistry has received much less attention, and the scope and limitations are poorly delineated despite the existence of several reports [11,12]. Furthermore, no reports on direct coupling with H_2S (or NaSH or Na_2S) have hitherto been published [4]. Therefore, in conjunction with our ongoing research on our drug candidate, these circumstances prompted us to investigate cross-coupling reaction of aryl bromides and triflates with arylthiols and thiol surrogates in a more systematic manner.

PALLADIUM-CATALYZED AROMATIC C–S BOND FORMATION

The use of sulfur in transition-metal-catalyzed reactions is often avoided, owing to the notorious reputation of this element as a poison in such processes, exemplified by the classical Lindlar's catalyst. Accordingly, transition-metal-catalyzed sulfurization itself is a challenging issue to be addressed. Since Migita has pioneeringly reported the coupling of iodo- and bromoarenes with thiols using $Pd(PPh_3)_4$ as a catalyst in 1980 [11], several reports have appeared in the literature describing the formation of arylsulfides using transition-metal catalysts like Pd, Ni, and Cu [12]. However, in most cases, aryl iodides were employed rather than aryl bromides and triflates, and successful coupling of substrates and the partners was not only unclear but also very limited. The feasibility of the reaction is strongly influenced by the structures of the substrates and their coupling partners, but the scope and limitations have not yet been well delineated. Although aryl sulfides are a common functional feature of numerous biologically active compounds, traditional methods are still used frequently for formation of the aryl C–S bond [13].

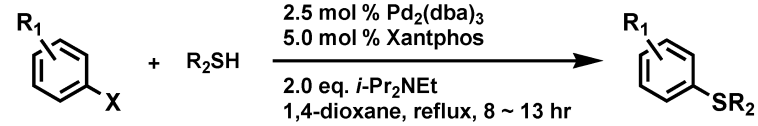
Given this background, in order to find a general catalyst system we selected Pd as a metal, bromobenzene as substrate, and 4-methoxyphenylmethylthiol (MPMSH) as partner, and screened a number of phosphine ligands, bases, solvents, and reaction temperatures for preliminary optimization. After extensive screening efforts, including several representative conditions reported, we found that the catalyst system prepared from $Pd_2(dba)_3$ and xantphos [14] led to a complete conversion with *i*-Pr_2NEt as base in dioxane after 6 h at reflux temperature as shown in Scheme 2 [15,16].



Scheme 2 Pd/xantphos-catalyzed aromatic sulfurization.

With the Pd/xantphos conditions in hand, to see the generality of this condition, we then looked into the tolerability of these conditions for the coupling reactions of various aryl bromides, chlorides, and triflates with aryl and alkylthiols. The results are summarized in Table 1. In terms of substituents R_1 on the phenyl ring, electron-withdrawing and -donating groups at 2- or 4-position were tolerated. As for leaving groups on the phenyl ring in the substrates, Br and OTf were also well tolerated. Cl was also tolerable when it was activated with electron-withdrawing groups as nitro and trifluoromethyl groups at 4-position. For the substituents of the coupling partners, not only alkyl groups but also aryl groups were tolerated very well, and even the sterically bulky *o*-isopropylphenyl or cyclohexyl groups resulted in good yields. Overall, these conditions generally worked very well on the sulfur version of the hetero cross-coupling reaction. Although the reactions were run with 5.0 mol % of the Pd and 5.0 mol % of xantphos, the actual catalyst loading may be much lower because some representative examples show good activity with below 1.0 mol % [15].

Table 1 Tolerability of Pd/xantphos system for cross-coupling of ArX with ArSH/AlkylSH.



X = Br, OTf, Cl

R_1	X	R_2	Yield (%)
H	Br	Ph	85
4-Ac	Br	Ph	90
4-MeO	Br	Ph	72
2-Me	Br	Ph	70
H	Br	2-*i*-Pr-Ph	88
H	Br	cyclo-hexyl	80
H	OTf	Ph	90
4-Me	OTf	Ph	79
4-NO_2	Cl	Ph	85

To understand why the Pd/xantphos system provided good results, coupling reactions with several representative monodentate and bidentate ligands were run under the same reaction conditions for the purpose of direct comparison. The results are shown in Fig. 1. All of the monodentate ligands gave the desired product in poor yields, and simultaneously formed two side products, disulfide (MPMS–SMPM) and benzene. Bidentate ligands, BINAP and DPPP, did not show any clear advantage over the monodentate ligands. However, ferrocenyl phosphine ligand, DPPF, greatly improved the yield, and concomitantly suppressed formation of two side products in low yields. Faster reaction rates for the

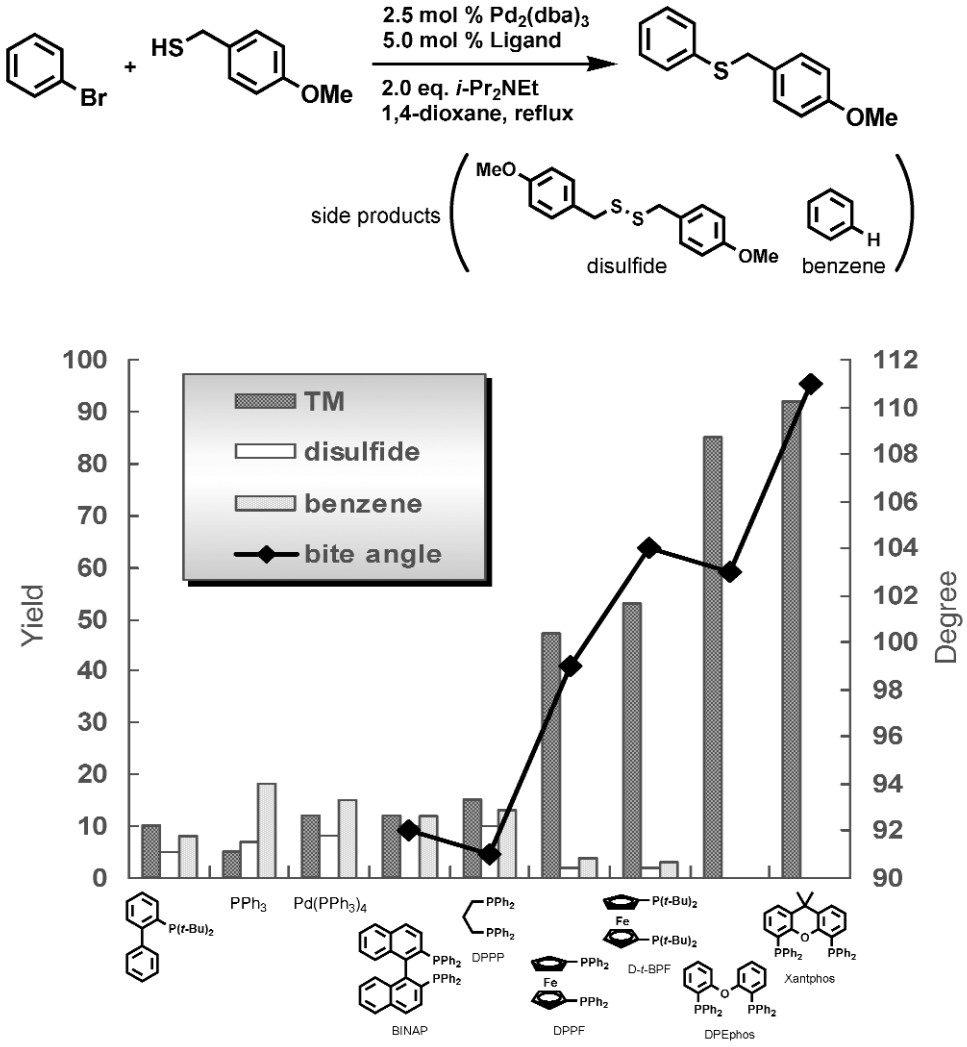


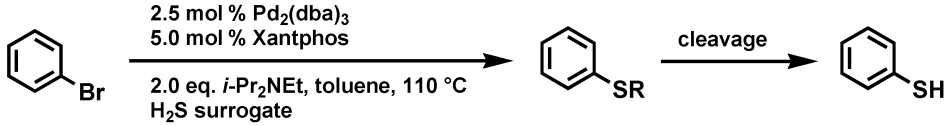
Fig. 1 Comparison of the yields of the products and their bite angles among representative monodentate and bidentate ligands.

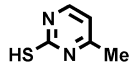
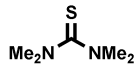
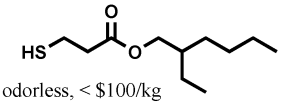
desired pathway can suppress oxidation to the disulfide, and acceleration of the reductive elimination step prevents formation of benzene via β-hydride elimination. More bulky and electronically donating D-*t*-BPF, which Hartwig successfully used for aromatic amination, further improved the yield [17]. DPEphos dramatically improved the yield [12b], and xantphos was the best. Although these results seemed to indicate that bidentate ligands with larger bite angles resulted in better yields, a discrepancy between D-*t*-BPF and DPEphos was observed. In this regard, two years after our studies, in 2006, very interestingly, Hartwig demonstrated that CyPF-*t*-Bu (Josiphos ligand, (*R*)-(–)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine) worked very efficiently for aromatic amination [17,18] and sulfurization [19].

COUPLING REACTIONS WITH H_2S SURROGATES

With the Pd/xantphos system in hand, we selected several H_2S surrogates and conducted the coupling reaction under the same conditions. The results are depicted in Table 2. The first trial with atom-efficient Na_2S did not give any desired product, unfortunately. Reactions with urea [20], silylthiol [21], and thiobenzoic acid [22] were also sluggish. However, as mentioned above, reaction with MPMSH afforded the coupling product in 92 % yield, which was easily cleaved under a mild acidic condition to give the desired thiophenol in 90 % yield. In addition, 2-ethylhexyl 3-mercaptopropionate [23], which is odorless, inexpensive, and readily available on an industrial scale, was also found to be excellent for this purpose. The coupling reaction afforded the corresponding sulfide in 88 % yield, which was easily cleaved under mildly basic conditions to give thiophenol in quantitative yield. These two surrogates should be chosen according to their susceptibilities, in other words, stabilities as protecting groups in the downstream chemistry. Either surrogate is tolerated under acidic or basic conditions. Furthermore, combination of these surrogates with other cross-coupling reactions like Suzuki/Miyaura, Sonogashira, Heck, and Buchwald/Hartwig-type cross couplings will allow us to expand an opportunity to prepare sulfur-containing biologically active compounds [24].

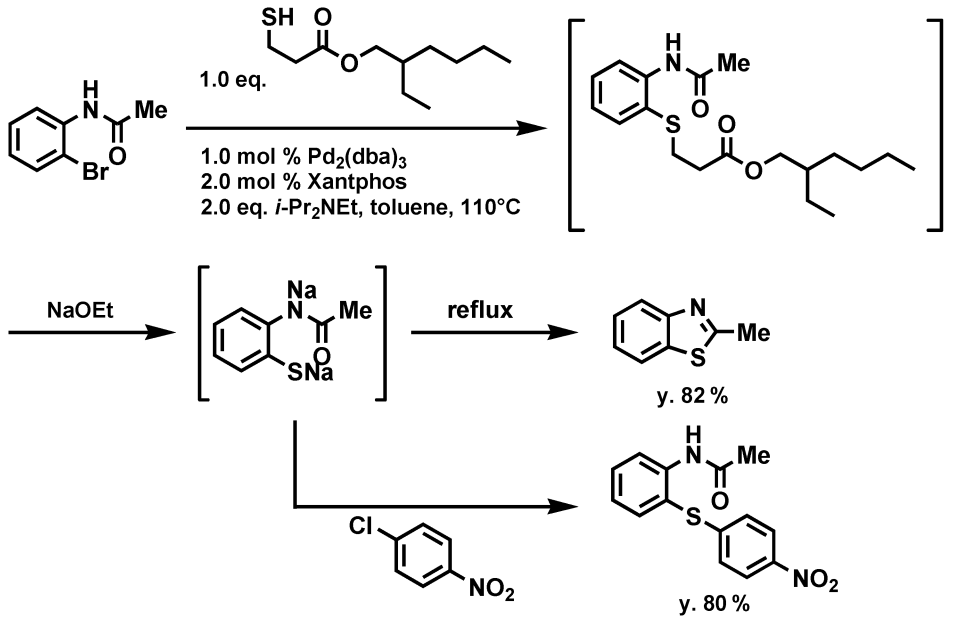
Table 2 Coupling reaction with several H_2S surrogates.



H_2S surrogate	PhSR	Cleavage	PhSH
Na_2S	ND	Acidic	N/A
	5 %	Acidic	N/A
$HSSi(i\text{-}Pr)_3$	20 %	Acidic	N/A
HSMPM	92 %	Acidic	90 %
HSCOPh	10 %	Basic	N/A
	10 %	Basic	N/A
 odorless, < $100/kg	88 %	Basic	Quant.

PRACTICAL SYNTHESIS OF BENZOTHIAZOLES VIA PALLADIUM-CATALYZED CROSS-COUPLING WITH THIOL

With good surrogates like 2-ethylhexyl 3-mercaptopropionate in hand, we finally investigated approaches to the synthesis of benzothiazole. In the initial study for the preparation of sulfide, we carried out the reaction of 2-bromoacetanilide with the mercaptopropionate surrogate catalyzed by $Pd_2(dba)_3$/xantphos system to give the corresponding sulfide in good yield. The resulting sulfide was treated with NaOEt in EtOH at room temperature to form the sodium thiolate followed by heating at reflux to afford 2-methylbenzothiazole in 82 % yield as described in Scheme 3 [25]. The sodium thiolate can be used for some other transformations. For example, 4-chloronitrobenzene underwent S_NAr reaction with thiolate to give the desired sulfide adduct in 80 % yield [26]. Encouraged by these results, the scope and limitation was further investigated.



Scheme 3 Synthesis of benzothiazoles via Pd-catalyzed coupling of mercaptopropionate followed by deprotection and condensation.

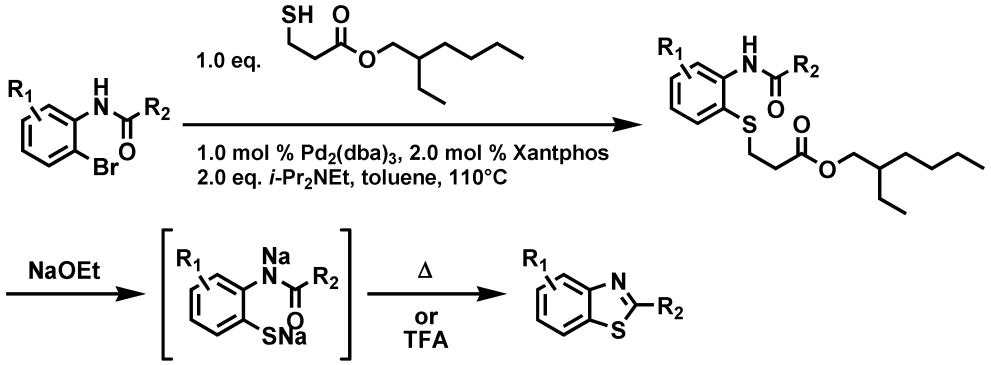
As shown in Table 3, various 2-bromobenzanilides were successfully converted into the corresponding benzothiazoles in good yields via C–S bond formation followed by sequential deprotection and condensation. The yields of C–S bond formation did not depend on the substrates and were high in most cases, however, the results and the conditions of the intramolecular condensation depended on the substrates. The substrates possessing carbonyl groups of the amides activated by the electron-withdrawing group were rapidly cyclized under basic conditions at reflux temperature. Bromoacetanilides displayed borderline reactivity toward cyclization. Some could be cyclized, but others could not (entries 3 and 4 vs. entries 5 and 6). When the amide was affected by an electron-donating group, the yield of the condensation product was quite low under basic conditions (entry 8). By contrast, the acidic conditions were more effective for this cyclization. If trifluoroacetyl (TFA) was used for the cyclization, all substrates listed in the table resulted in good yields of the desired products. The substrates having keto-functionalities in their molecules gave the corresponding benzothiazoles in high yield (entries 4 and 6).

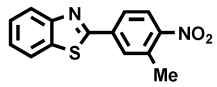
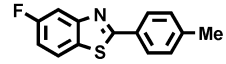
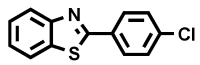
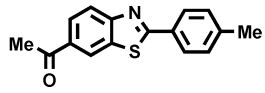
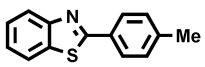
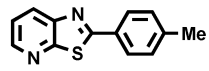
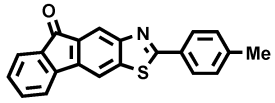
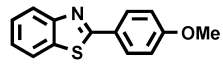
On the other hand, in the case of the reaction of a substrate which is labile under basic conditions, the reaction with MPMSH was also demonstrated successfully [24].

In summary, the C–S bond formation of aryl bromides and triflates catalyzed by the Pd/xantphos system has been demonstrated. Based on this finding, a novel and practical synthesis of benzothiazoles has been developed. To the best of our knowledge, this is the first report of the synthesis of benzothiazole via Pd-catalyzed coupling reaction of bromoarenes with thiol surrogates. This new methodology allows us to assemble a wide range, not only of benzothiazoles, but also of benzimidazoles without any substituent at the nitrogen.

The scope of this methodology is being expanded to include synthesis of thiazoles possessing a stereogenic center at the α-position. These results will be published elsewhere.

Table 3 Synthesis of benzothiazoles.



Entry	Thiazole	NaOEt, Δ (TFA)	Entry	Thiazole	NaOEt, Δ (TFA)
1		75 % (77 %)	5		low (75 %)
2		83 % (81 %)	6		low (84 %)
3		82 % (80 %)	7		low (67 %)
4		72 % (71 %)	8		low (85 %)

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