One-Pot Thiourea Formation–Palladium-Catalyzed Cyclization Sequence to 3,4-Dihydro-2*H*-1,3-benzothiazine-2-imines from 2-Halo *N*-Methylbenzylamine – Scope and Limitations

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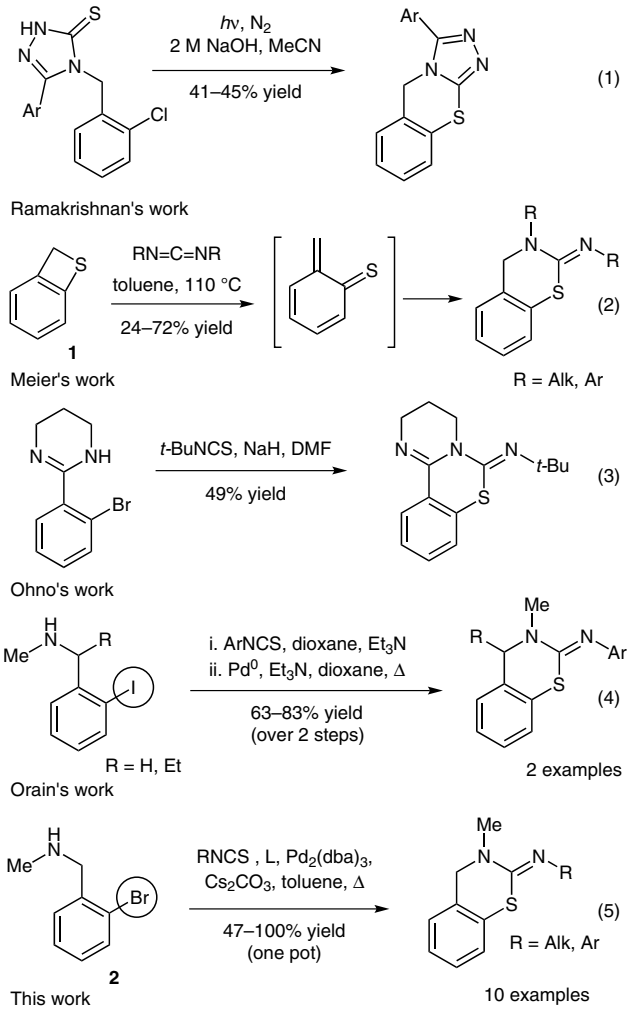
Abstract: A practical synthesis of 3,4-dihydro-3-methyl-2*H*-1,3-benzothiazine-2-imine via intramolecular palladium-catalyzed C–S bond formation is presented and exemplified for both alkyl- and arylisothiocyanates.

Key words: palladium, heterocycles, sulfur, ring closure, catalysis

In the course of a recent research program, a direct synthesis of a series of 3,4-dihydro-3-methyl-2*H*-1,3-benzothiazine-2-imines, that would be amenable to parallel synthesis, was required. According to the literature, the 3,4-dihydro-2*H*-1,3-benzothiazine-2-imine motif can be accessed via photocyclization of an anionic thiocarbonyl sulfur species with a proximate chloroarene moiety (Scheme 1, equation 1),[1] or by tandem pyrolysis of 2*H*-benzo[*b*]thiet **1**[2] and [8π + 2π] hetero Diels–Alder cycloaddition with *N*,*N*′-dialkyl or diarylcarbodiimide dipolarophiles (Scheme 1, equation 2).[3] However, neither of those approaches conveniently introduces diversity at the C2 imine position. A broader variation on the 3,4-dihydro-2*H*-1,3-benzothiazine-2-imine core was described by Ohno with a one-pot thiourea formation and key intramolecular S_NAr on a bromoarene scaffold to set up the carbon–sulfur bond (Scheme 1, equation 3).[4] Noticeably, the reported S_NAr proved to be effective only with an activated bromoarene having a σ- or π-acceptor substituent in the *ortho* position, which is in turn a clear limitation.[5] In a recent alternative, Orain et al. published a two-step synthesis of 3,4-dihydro-2*H*-1,3-benzothiazine-2-imines from 2-iodo *N*-methyl benzylamine derivatives and substituted phenylisothiocyanates. In this process, limited to the use of arylisothiocyanates, the key C–S bond was set up through a regioselective intramolecular palladium-mediated cyclization between the thiourea moiety and the iodoarene (Scheme 1, equation 4).[6] Although this route is suitable for a late-stage incorporation of a C2 imine substituent, we felt there was still significant room for improvement: firstly to achieve a more practical one-pot process; whereby the intermediate thiourea would not be isolated. Secondly, from a methodological viewpoint, the use of the less expensive 2-bromo *N*-methylbenzylamine (**2**) compared to the less readily available 2-iodo analogue would permit extension of scope to further variations on the core structure. Only two examples of related intramolecular palladium-mediated thiourea cyclization from bromoarenes have been reported, with variable yield.[6,7] In this letter, we present a concise route that is amenable to the introduction of both alkyl- and arylisothiocyanates as highly variable substrates (Scheme 1, equation 5). Opti-



Scheme 1 Various synthetic approaches towards the 3,4-dihydro-3-methyl-2*H*-1,3-benzothiazine-2-imine motif

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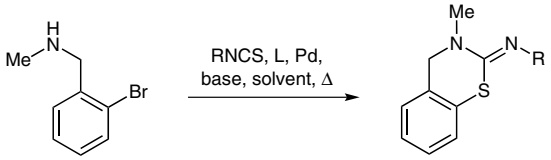
mization of our novel one-pot two-step process was initiated by reacting **2** with cyclohexyl isothiocyanate as a model substrate (Table 1, entry 1). Initial assessment of the two previously reported conditions for intramolecular thiourea C–S bond formation with bromoarenes resulted in disappointing outcomes.

Table 1 Synthesis of 3,4-Dihydro-3-methyl-2*H*-1,3-benzothiazine-2-imine



2 **3a–j**

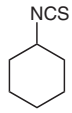
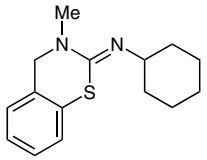
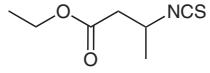
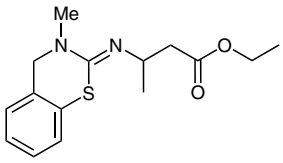
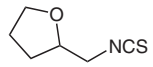
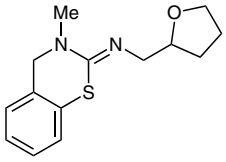
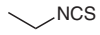
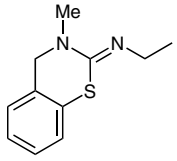
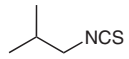
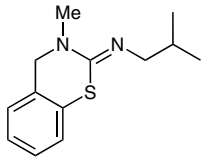
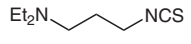
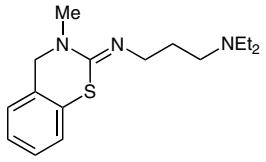
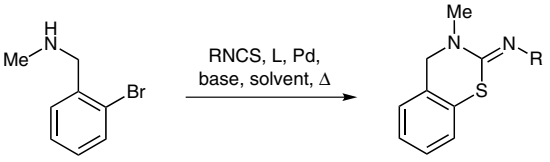
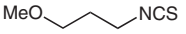
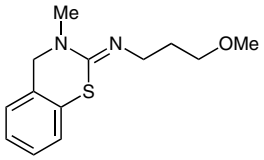
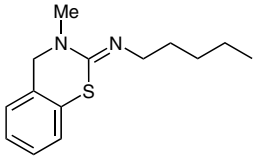
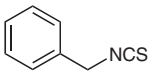
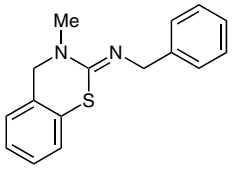
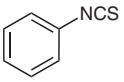
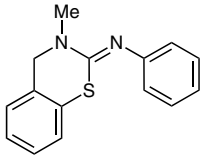
Entry	RNCS	Product	Yield (%)[a]
1		 **3a**	100[b] –[c] (26)[d] (57)[e]
2		 **3b**	78[b]
3		 **3c**	95[b]
4		 **3d**	47[b]
5		 **3e**	97[b]
6		 **3f**	87[b]

Table 1 Synthesis of 3,4-Dihydro-3-methyl-2*H*-1,3-benzothiazine-2-imine (continued)



2 **3a–j**

Entry	RNCS	Product	Yield (%)[a]
7		 **3g**	77[b]
8		 **3h**	82[b]
9		 **3i**	34[b] 66[f]
10		 **3j**	–[b] 57[f]

[a] Isolated yields.

[b] Unless otherwise noted all the reactions were performed in a sealed vessel with **2** (0.7 mmol), RNCS (1.1 equiv), Cs_2CO_3 (2.2 equiv), $Pd_2(dba)_3$ (0.05 equiv), and Xantphos (0.1 equiv) in dry degassed toluene (1.4–1.5 mL) at 100–105 °C for 8–16 h.

[c] Control reaction: same conditions as b) but without any ligand and palladium source.

[d] Conversion by HPLC at λ = 254 nm for the following reaction conditions: **2** (0.7 mmol), RNCS (1.1 equiv), Et_3N (2.0 equiv), $Pd[PPh_3]_4$ (0.10 equiv), Ph_3P (0.10 equiv) in dry degassed dioxane (1.2–1.3 mL) at 100 °C for 16 h.

[e] Conversion by HPLC at λ = 254 nm for the following reaction conditions: **2** (0.7 mmol), RNCS (1.1 equiv), Cs_2CO_3 (2.2 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (0.10 equiv) in dry degassed dioxane (1.2–1.3 mL) at 95–100 °C for 16 h.

[f] Reaction conditions: **2** (0.7 mmol), RNCS (1.1 equiv), Cs_2CO_3 (2.7 equiv), $Pd_2(dba)_3$ (0.12–0.15 equiv) and DPPF (0.25–0.30 equiv) in dry degassed toluene (1.5 mL) at 125–130 °C for 24–32 h.

Thus, a combination of monodendate ligand Ph_3P with Et_3N in refluxing dioxane led to a sluggish reaction and modest conversion. Alternatively, a mixture of strongly basic and hindered Fu's phosphine [$P(t\text{-}Bu)_3$] and Cs_2CO_3

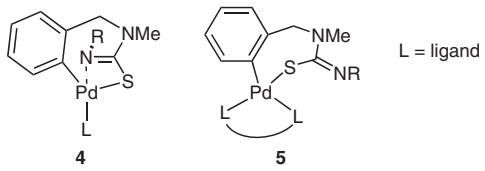
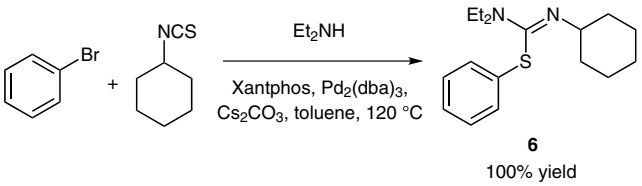


Figure 1 Putative κ^2-'isothioamidate'complex **4** and κ^1-'isothioamidate'complex **5**

in dioxane afforded better conversions (still less than two thirds), but the reaction did not proceed to completion at 100 °C. By analogy with the known reluctance of arylamidate complexes to undergo fast reductive elimination from palladium^{II} due to κ^2-amidate coordination,[8] we hypothesized that a putative κ^2-'isothioamidate-type' complex **4** may arise in the catalytic cycle (Figure 1), thus inhibiting reductive elimination and therefore catalytic turnover. It has also been shown that the use of large-bite-angle bidendate ligands prevents κ^2-binding modes.[9]

Gratifyingly, we found that a system of Xantphos, $Pd_2(dba)_3$, and Cs_2CO_3 in toluene afforded **3a** in quantitative yield. To rule out a possible thiourea cyclization driven by S_NAr, a control experiment was carried out under similar conditions, omitting the catalytic system and, as expected, no trace of **3a** was found. Our protocol was next exemplified with a range of alkyl isothiocyanates (Table 1, entries 2–8), providing the corresponding 3,4-dihydro-2*H*-1,3-benzothiazine-2-imines **3b**–**h** in moderate to excellent yields.[10] Notably, esters and basic groups were tolerated in the reaction. Unfortunately, phenyl- and to a lesser extent benzyl isothiocyanates reacted poorly under those conditions (Table 1, entries 9 and 10). This trend was assigned to both a lower nucleophilicity of the intermediate thiourea and an increased ionic character of the Pd^{II} 'isothioamidate' complex leading to a stronger Pd–S bond.[9] The reductive elimination was therefore slower and occurred in very low yield. Eventually, we were able to achieve reasonable conversion rates and deliver products **3i**–**j** in acceptable yields by increasing temperature, reaction time, catalyst loading, and using DPPF as an alternative ligand. Although we cannot provide a clear explanation for this ligand effect, we suggest that the chelating bidendate ligand maintains a fast rate of reductive elimination for steric reasons – in other words, by enforcement of *cis* geometry and angle minimization between the two metal-bound substituents. Electronic factors in this case cannot be invoked since DPPF is more electron donating than Xantphos and thus tends to disfavor reductive elimination.[11,12] A control experiment was next conducted in order to probe whether intramolecularity plays a role in the key C–S bond formation. Thus, a mixture of bromobenzene, diethylamine, and cyclohexyl isothiocyanate was reacted under standard conditions to deliver the arylated isothiourea **6** in quantitative yield (Scheme 2). Apparently, intramolecularity is not a key driver for the coupling. We believe that the wide-bite-angle bidendate chelating ligand imposes a great steric strain on the seven-membered ring isothioamidate complex **5**, promoting fast reductive elimination of palladium-bound substituents. The associated cost in energy could somehow compensate for favorable six-membered ring formation.



Scheme 2 Intermolecular palladium-catalyzed isothiourea coupling with bromobenzene

In order to expand the scope of the reaction to commercially available chloroarene **7**, several attempts using monodendate ligands were performed but all met with failure (Scheme 3). More specifically, reactions conducted in the presence of commercially available bipyrazole BippyPhos (Figure 2),[13] or Buchwald's XPhos, ligands, known to promote, respectively, smooth intermolecular coupling of chloroarenes with phenylureas, and intermolecular *o*-chloroanilines urea cyclizations afforded **3a** only in trace amounts.[14,15] It is recognized that both sterically demanding ligands facilitate dissociation to monophosphine–palladium adducts to which the chloroarene rapidly oxidatively adds as a result of the phosphine electron density.[16,17] In addition, coordination of the isothiourea with the monophosphine LPd(Ar)Cl complex should also be faster relative to the coordinatively saturated $L_2Pd(Ar)Cl$ complex.[8] Therefore, the poor results observed in this C–S bond formation may again stem from problematic reductive elimination.

In conclusion, a simple procedure to rapidly access the 3,4-dihydro-2*H*-1,3-benzothiazine-2-imine motif in the *o*-bromoarene series has been developed using Pd^0 chem-

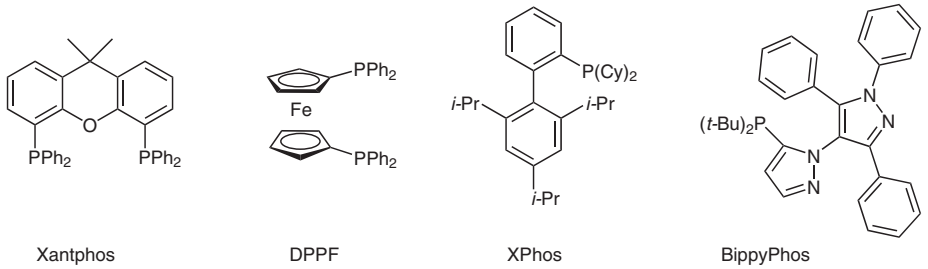
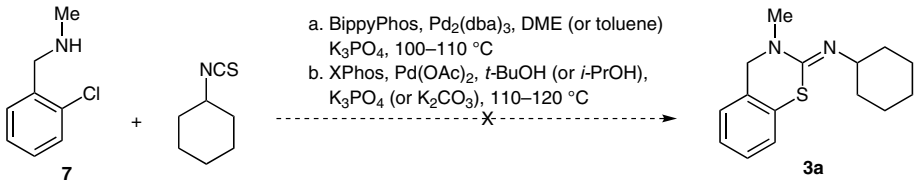


Figure 2 Ligands used for Pd^0-catalyzed isothiourea arylation



Scheme 3 Attempted palladium-mediated C–S bond formation from chloroarene **7**

istry and validated with both alkyl- and arylisothiocyanates. Utilization of wide-bite-angle bidendate ligands was found to be crucial for successful outcomes. Application of the current methodology to substituted *o*-bromo *N*-alkyl benzylamine substrates is under way and will be reported in due course.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) Senthilvelan, A.; Ramanakrishnan, V. T. *Tetrahedron Lett.* **2002**, 5119.
(2) Voigt, E.; Meier, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 117.
(3) Groelsch, D.; Niedermann, H. P.; Meier, H. *Chem. Ber.* **1994**, *127*, 955.
(4) Mizuhara, T.; Oishi, S.; Fujii, N.; Ohnon, H. *J. Org. Chem.* **2010**, *75*, 265.
(5) For references on the thermal synthesis of 2-amino benzothiazoles via base-promoted cyclization of *o*-bromophenylthiourea and the rationale about factors involved in such a S_NAr activation, see: (a) Feng, E.; Huang, H.; Zhou, Y.; Ye, D.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2010**, *12*, 422. (b) Ding, Q.; Huang, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 1047.
(6) Orain, D.; Blumstein, A.; Tasdelen, E.; Haessig, S. *Synlett* **2008**, 2433.
(7) Hardy, S.; Martin, S. F. *Org. Lett.* **2011**, *13*, 3102.
(8) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.
(9) Fujita, K.; Yamashita, M.; Puschmann, F.; Alvarez-Falcon, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044.
(10) For a general procedure and spectroscopic data for final compounds **3a**–**j**, see the Supporting Information.
(11) Hammann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.
(12) Suparabhorn, S.; Lange, S.; Chen, W.; Xiao, J. *J. Mol. Catal. A* **2003**, *196*, 125.
(13) Singer, R. A.; Dore, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* **2006**, *47*, 3727.
(14) Kotecki, B. J.; Fernando, D. P.; Haight, A. R.; Lukin, K. A. *Org. Lett.* **2009**, *11*, 947.
(15) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311.
(16) Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.
(17) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417.

