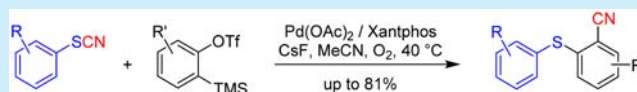


Activation of Aryl Thiocyanates Followed by Aryne Insertion: Access to 1,2-Thiobenzonitriles

Martin Pawliczek,^{†,‡} Lennart K. B. Garve,[†] and Daniel B. Werz^{*,†}[†]Technische Universität Braunschweig, Institut für Organische Chemie, Hagenring 30, 38106 Braunschweig, Germany[‡]Georg-August-Universität Göttingen, Institut für Organische und Biomolekulare Chemie, Tammannstraße 2, 37077 Göttingen, Germany

Supporting Information

ABSTRACT: Palladium-catalyzed activation of carbon–sulfur bonds allows aryne insertion into aryl thiocyanates to generate new C–SAr and C–CN bonds in one step. The readily available starting materials make this method efficient in generating a variety of 1,2-thiobenzonitriles. By choosing an oxygen atmosphere the yields are increased and side reactions are minimized.



The development of novel methodologies to form carbon–sulfur bonds is crucial for the synthesis and derivatization of target molecules in pharmaceutical and material science.¹ Important classes of sulfur-containing compounds are biaryl sulfides and their higher oxidized homologues. For that purpose, several methods have been described utilizing transition metal² or transition-metal-free³ conditions to prepare the biaryl thioether moiety. Most of these approaches predominantly tackle the problem to generate the carbon–sulfur bond (e.g., by nucleophilic aromatic substitution), generating one bond in one step. However, it is desirable to find novel synthetic methods to install additional functionalities concomitant with the formation of the carbon–sulfur bond. Recently, transition-metal catalyzed intramolecular oxycyanation and aminocyanation⁴ reactions of alkenes and intermolecular cyanothiolation⁵ of terminal alkynes were reported. After the cleavage of the Het–CN bond, new C–Het and C–CN bonds were formed.

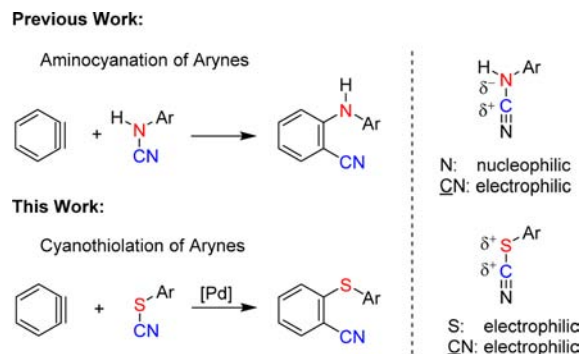
In 2014, Rao and Zeng were able to convert arynes with cyanamides resulting in a simultaneous C–N and C–CN bond formation in one step (Scheme 1).⁶ No activation of the N–CN bond by a transition metal was required. Intrigued by this

simple reaction, we asked ourselves whether other Het–CN bonds such as S–CN are able to undergo a similar transformation. In contrast to the reactivity of Het–CN bonds with alkenes or alkynes the strained triple bond of an aryne possesses a much higher reactivity; thus, numerous side reactions such as triphenylene formation⁷ have to be suppressed using this special kind of triple bond as a reaction partner.

A major difference between cyanamides and thiocyanates is the philicity of the two heteroatoms. The facile loss of the acidic hydrogen of cyanamides renders the internal nitrogen highly nucleophilic and enables attack to the electrophilic aryne without further activation (Scheme 1).⁸ Contrary to nitrogen in cyanamides, the sulfur in thiocyanates is rather positively polarized⁹ and is not able to undergo a nucleophilic attack on the aryne without further activation. Therefore, we tried to combine aryne chemistry¹⁰ with a Pd-catalyzed activation of aryl thiocyanates.

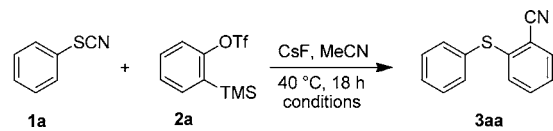
At the outset of our studies phenyl thiocyanate (**1a**) and aryne precursor **2a** were reacted under standard conditions commonly employed in aryne chemistry using CsF and acetonitrile at 40 °C (Table 1, entry 1). As expected, even after heating up to 80 °C, the desired coupling product could not be detected, but complete consumption of **2a** was observed. Application of Pd(PPh₃)₄ as a catalyst yielded traces of product **3aa** with concomitant formation of diphenylthioether as the major product (Table 1, entry 2). Therefore, Pd(OAc)₂ in combination with Xantphos was applied affording **3aa** in yields varying between 10% and 30% (Table 1, entry 3). Surprisingly, oxidative reaction conditions using an oxygen atmosphere dramatically increased the yield to 81% (Table 1, entry 4). In addition, the formation of diphenylthioether was suppressed (<10%) and the time for full substrate consumption could be lowered from 54 to 18 h. Further attempts to improve the

Scheme 1. Insertion of Arynes into Het–CN Bonds



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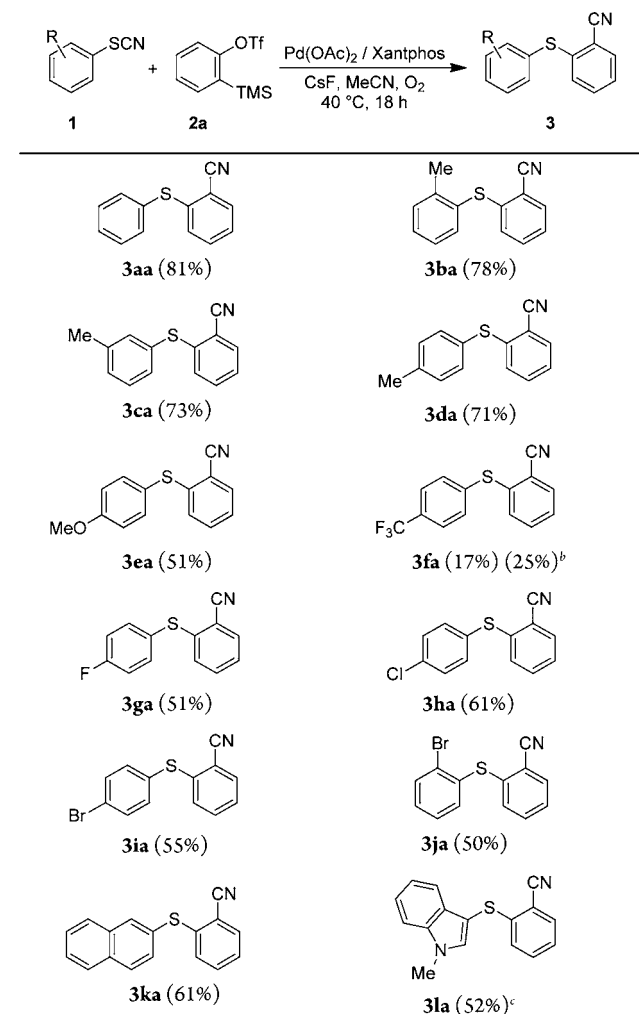
Table 1. Screening of Reaction Conditions^a


entry	catalyst (10 mol %)	ligand (mol %)	atmosphere	yield (%)
1 ^b	—	—	Ar or O ₂	0
2	Pd(PPh ₃) ₄	—	Ar	traces
3 ^c	Pd(OAc) ₂	Xantphos (20)	Ar	10–30
5	Pd(OAc) ₂	Xantphos (20)	O ₂	81
6	Pd(OAc) ₂	Xantphos (15)	O ₂	42
7	Pd(OAc) ₂	PPh ₃ (20)	O ₂	0
8	Pd(OAc) ₂	dppf (20)	O ₂	0
9	Pd(OAc) ₂	dppp (20)	O ₂	traces
10	Pd(OAc) ₂	—	O ₂	0
11	—	Xantphos (20)	O ₂	0
12	Pd(OAc) ₂	Xantphos (20)	air	41

^aReaction conditions: **1a** (13.2 mg, 100 μ mol, 1.0 equiv), **2a** (34.0 μ L, 140 μ mol, 1.4 equiv), CsF (50.0 mg, 330 μ mol, 3.3 equiv), MeCN (4 mL) at 40 °C for 18 h. ^bReaction temperature 40 and 80 °C. ^cReaction time 54 h.

reaction conditions by applying a lesser amount of Xantphos or different ligand systems significantly decreased the yield or proved to be completely unsuccessful (Table 1, entries 6–9). Utilizing either Pd(OAc)₂ or Xantphos yielded 0% of **3aa**, respectively (Table 1, entries 10 and 11). The use of air instead of an oxygen atmosphere was less successful and afforded the product in only 41% yield (Table 1, entry 12). Moreover, to prevent triphenylene formation the slow or stepwise addition of **2a** was not necessary. The catalytic system in combination with phenyl thiocyanate bypasses this undesired reaction pathway. Other common oxidants such as benzoquinone, silver carbonate, and copper(II) acetate entirely suppressed the product formation. Application of oxone and ammonium persulfate had no influence on the reaction and afforded the product in similar yields as when under an argon atmosphere.

With the optimized reaction conditions in hand we started to examine the scope of this transformation (Scheme 2). Various electron-donating and -withdrawing aryl thiocyanates were exposed to the reaction. Methyl substituents in *ortho*-, *meta*-, and *para*-positions yielded the corresponding thiobenzonitriles in similar yields ranging from 71% to 78% (**3ba**–**3da**). Application of the electron-donating but inductively electron-withdrawing anisole derivative delivered the corresponding product **3ea** in 51% yield. The electron-poor phenyl thiocyanate containing the electron-withdrawing CF₃ group was converted to the desired product **3fa** in only 17% yield. Decreasing the reaction temperature to 25 °C increased the yield up to 25%. Different halogens at the benzene ring revealed only a small influence on the reactivity. The desired products could be obtained in moderate yields ranging from 50% to 61% (**3ga**–**3ja**). However, these examples represent products which show difficulties in several other biaryl thioether syntheses. Finally, thiocyanates with extended π -systems were employed affording naphthalene derivative **3ka** in 61% yield and indole derivative **3la** in 52% yield, respectively. In contrast to previous examples trimerization of the aryne was a noteworthy side reaction. Because of the formation of a large amount of triphenylene side product, 4.5 equiv of **2a** were required to achieve a satisfactory conversion in the latter case.

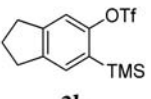
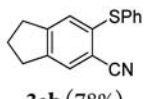
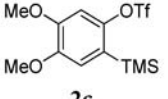
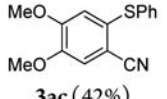
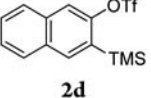
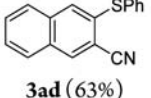
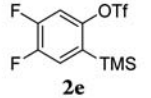
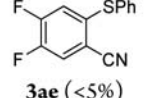
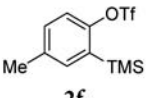
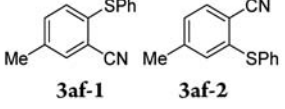
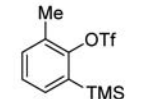
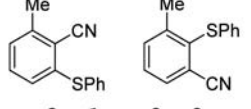
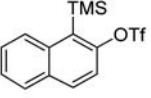
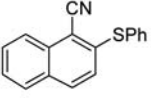
Scheme 2. Scope with Respect to ArSCN^a

^aReaction conditions: **1** (13.2 mg, 100 μ mol, 1.0 equiv), **2a** (34.0 μ L, 140 μ mol, 1.4 equiv), Pd(OAc)₂ (2.2 mg, 10.0 μ mol, 10 mol %), Xantphos (11.6 mg, 20.0 μ mol, 20 mol %), CsF (50.0 mg, 330 μ mol, 3.3 equiv), MeCN (4 mL) at 40 °C for 18 h under O₂ atmosphere. ^bReaction temperature 25 °C. ^c4.5 equiv of **2a** were applied.

Afterward, we extended the scope of the 1,2-functionalization with respect to the aryne (Table 2). Gratefully, electron-rich, inductively electron-withdrawing arynes and those with expanded π -systems could be converted to the corresponding 1,2-difunctionalized products in 42–78% yield (Table 2, entries 1–3). Unfortunately, when using **2e** bearing two fluorine substituents, the desired thiobenzonitrile **3ae** was only observed by GC-MS in less than 5% yield (Table 2, entry 4), although **2e** was entirely consumed concomitant with mostly untouched phenyl thiocyanate. In addition, when unsymmetrical aryne precursors were employed, regioisomeric mixtures were obtained in 45% up to 79% yield (Table 2, entries 5–7). Noteworthy, in the cases of **2g** and **2h** the major isomers contain the small nitrile residue next to the sterically encumbered position as unequivocally shown by 2D-NMR spectroscopic investigations.

To elucidate the mechanistic scenario we tried to capture reaction intermediates. Therefore, phenylacetylene or styrene, respectively, were added to trap the reactive species after the first bond forming step has occurred through either carbo- or thiopalladation. Unfortunately, exclusively thiobenzonitrile **3aa**

Table 2. Scope with Respect to Aryne^a

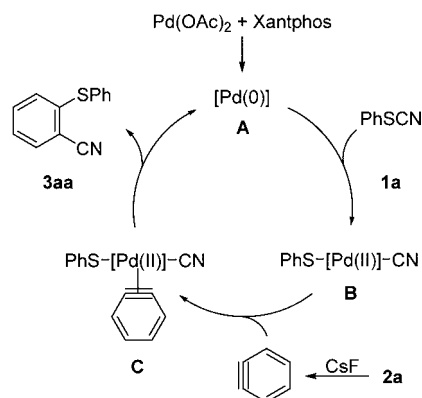
aryne precursor	product
<p>1</p>  <p>2b</p>	<p>3ab (78%)</p> 
<p>2</p>  <p>2c</p>	<p>3ac (42%)</p> 
<p>3</p>  <p>2d</p>	<p>3ad (63%)</p> 
<p>4</p>  <p>2e</p>	<p>3ae (<5%)</p> 
<p>5</p>  <p>2f</p>	<p>3af-1 3af-2</p>  <p>(79%)^b</p>
<p>6</p>  <p>2g</p>	<p>3ag-1 3ag-2</p>  <p>(67%)^c</p>
<p>7</p>  <p>2h</p>	<p>3ah (44%)^d</p> 

^aReaction conditions: **1a** (13.2 mg, 100 μ mol, 1.0 equiv), **2** (34.0 μ L, 140 μ mol, 1.4 equiv), Pd(OAc)₂ (2.2 mg, 10.0 μ mol, 10 mol %), Xantphos (11.6 mg, 20.0 μ mol, 20 mol %), CsF (50.0 mg, 330 μ mol, 3.3 equiv), MeCN (4 mL) at 40 °C for 18 h under O₂ atmosphere. ^bRatio **3fa-1**/**3fa-2** = 1:1. ^cRatio **3ga-1**/**3ga-2** = 3:1. ^dMinor isomer could not be isolated, ratio >20:1.

was observed as the coupling product without incorporation of phenylacetylene or styrene (for details see Supporting Information).

Based on our experimental results and literature evidence,^{4,5,7} a plausible reaction mechanism is proposed in Scheme 3. The combination of Pd(OAc)₂ and Xantphos generates the active [Pd(0)] catalyst which undergoes oxidative addition into the PhS–CN bond to form intermediate **B**. Afterward, the aryne generated from **2a** and CsF is coordinated by the Pd center to afford species **C**. Finally, two bond forming steps of unknown order, consisting of a carbo- or thiometalation and reductive elimination, generate the desired 1,2-thiobenzonitrile **3aa**. During the last step the active [Pd(0)] species is regenerated. The role of the oxygen atmosphere is not really clear; however,

Scheme 3. Proposed Reaction Mechanism



we assume a stabilizing effect for an intermediate which is formed during the catalytic cycle rather than the occurrence of Pd(IV). Commonly, Pd(II)/Pd(IV) chemistry would require stronger oxidizing agents than oxygen.¹¹ Regarding the role of Xantphos we speculate that the large bite angle of this ligand facilitates the coordination of the aryne.

In conclusion, we developed a novel access to 1,2-thiobenzonitriles. Starting from aryne precursors and aryl thiocyanates the desired products were obtained in moderate to good yield. In consequence of its electronic properties the S–CN bond had to be activated for aryne insertion, wherefore palladium catalysis was employed. Choosing an oxygen atmosphere dramatically increased the yield, minimized the formation of side products, and significantly reduced the reaction time. This protocol provides a straightforward access to 1,2-thiobenzonitriles starting from readily available aryl thiocyanates and aryne precursors and serves as an alternative for the synthesis of biaryl thioethers.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, analytical data, and ¹H and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: d.werz@tu-braunschweig.de.

Notes

The authors declare no competing financial interest.

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