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# Pd- and Ni-Catalyzed Cross-Coupling Reactions of Functionalized Organozinc Reagents with Unsaturated Thioethers

Laurin Melzig, Albrecht Metzger, and Paul Knochel*[a]

**Abstract:** A variety of unsaturated thioethers have been subjected to cross-coupling reactions with functionalized zinc reagents in the presence of a transition-metal catalyst. Three different catalytic systems based on Pd(OAc)$_2$ or [Ni(acac)$_2$] and the ligands S-Phos or DPE-Phos gave the best results. N-Heterocyclic thioethers based on a pyridine, pyrimidine, pyrazine, pyridazine, triazine, benzothiazole, benzoxazole, pyrrole, or quinazoline ring, as well as thiomethylacetylenes, serve as electrophiles in this cross-coupling reaction. Aryl-, heteroaryl-, benzylic, and alkylzinc halides with sensitive functionalities, such as ester, nitrile, or ketone groups react at ambient temperature with unsaturated thioethers using a Ni catalyst. The corresponding Pd-catalyzed reactions require slightly higher temperatures. Large-scale cross-coupling experiments (10–20 mmol) with N-heterocycles are also reported.

**Keywords:** cross-coupling • heterocycles • homogeneous catalysis • nickel • palladium • zinc

## Introduction

The conversion of a carbon–sulfur bond into a carbon–carbon bond under transition-metal catalysis is a useful cross-coupling procedure, which is especially important when the corresponding organic halides are unstable or difficult to prepare. In 1979, the groups of Wenkert and Takei described the cross-coupling between unsaturated thioethers or thiols and Grignard reagents under nickel catalysis.[1] Later, Fukuyama and co-workers, and in particular Liebeskind and co-workers, extended the scope of this cross-coupling reaction, which led to a general ketone synthesis that involved reacting functionalized thioesters with organozinc reagents or organoboronic acids in the presence of a palladium catalyst.[2] Furthermore, organostannanes,[3] as well as organoindium reagents,[4] have also been used as nucleophilic partners for the direct synthesis of ketones starting from the corresponding thioesters. More recently, this Pd-catalyzed reaction has been modified to allow the coupling of organoboronic acids or organostannanes with heteroaromatic or alkynyl thioethers.[5] All of these cross-coupling reactions require stoichiometric amounts of Cu$^{I}$ salts to proceed. Zinc organometallics are very useful reagents for organic synthesis due to their high tolerance to a broad range of functional groups.[6] However, they have rarely been used for cross-coupling reactions with unsaturated thio derivatives.[7] Recently, we reported Pd- and Ni-catalyzed cross-coupling reactions of unsaturated heterocyclic[8] and alkynyl[9] thioethers with organozinc reagents under mild conditions. Herein, we report the full scope of these novel cross-coupling reactions.

## Results and Discussion

**Preparation of unsaturated thioethers**: Thioether-substituted N-heterocycles, as well as acetylenes can be easily prepared by several methods, as shown in Scheme 1. The thioether moiety can be attached to N-heterocycles by the direct substitution of a halogen atom using the corresponding thiolate. Thus, the chloro-substituted triazine **1a** reacted with sodium thiomethanolate in DMF or MeCN at 25 °C to provide the corresponding 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2a**) in 87 % yield (Scheme 1a).[8a] Alternatively, heterocycles may be metallated and then quenched with MeSSMe. Thus, *N*-methylpyrrole (**1b**) was lithiated with *n*BuLi[10] and the resulting lithium reagent was treated with dimethyl disulfide to afford 1-methyl-2-(methylthio)pyrrole (**2b**) in 68 % yield (Scheme 1b). The methylation of heterocyclic thiols constitutes another method. Thus, successive treatment of benzoxazole-2-thiol (**1c**) at 25 °C with sodium hydride and iodomethane gave 2-(methylthio)-1,3-benzoxazole (**2c**) in almost quantitative yield (Scheme 1c).[11] This methylation step could be combined with a condensation reaction.[12] The reaction of 4,4,4-trifluoro-1-(2-thienyl)butane-1,3-dione (**1d**) with thiourea, followed by the above steps with sodium hydride and iodomethane, gave the functionalized pyrimidine **2d** in 19 % overall yield (Scheme 1d). In the case of the polyfunctional alkynyl steroid **1e**,[13] deprotonation with *i*PrMgCl·LiCl[14] and subsequent treatment with *S*-methyl methanethiosulfonate afforded the thiomethylated ethynyl estradiol derivative **3a** in 83 % yield (Scheme 1e).[9]

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[a] L. Melzig, A. Metzger, Prof. Dr. P. Knochel
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 89-2180-77680
E-mail: paul.knochel@cup.uni-muenchen.de

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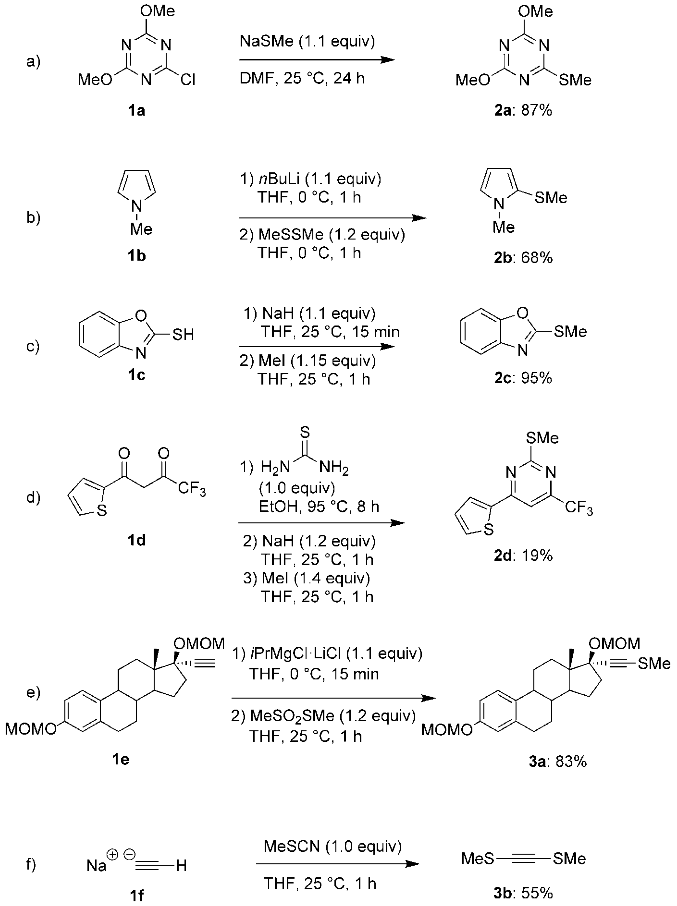
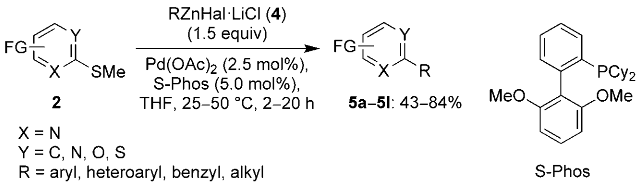


Scheme 1. Various pathways for the synthesis of unsaturated thioethers; MOM = methoxymethyl.

Bis(thiomethyl)acetylene (**3b**) was prepared in 55% yield by using sodium acetylide (**1f**) and methyl thiocyanate (25 °C, 1 h, Scheme 1f).[15] These various synthetic methods allowed us to prepare a variety of functionalized unsaturated thioethers, which were used in the subsequent Pd- and Ni-catalyzed cross-coupling reactions.

**Pd-catalyzed cross-coupling reactions of unsaturated N-heterocycles with organozinc reagents**: Pd$^0$-catalyzed cross-coupling reactions of functionalized aryl-, benzylic-, and alkylzinc reagents (1.5 equiv) with various thiomethyl-substituted N-heterocycles (1.0 equiv) were best carried out using Pd(OAc)$_2$/S-Phos as the catalytic system. This efficient combination was originally introduced by Buchwald[16] (Scheme 2). Most of the reactions described herein were carried out at 25 °C within 2–20 h.

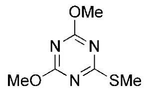
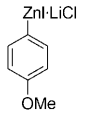
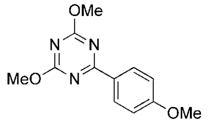
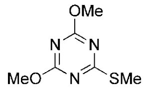
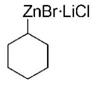
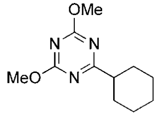
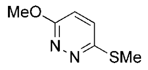
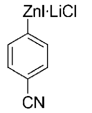
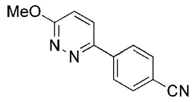
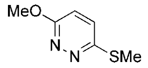
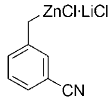
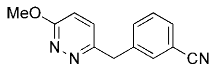
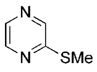
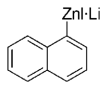
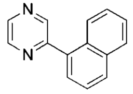
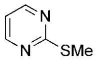
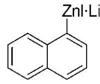
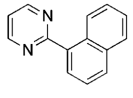
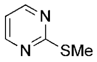
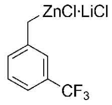
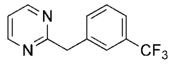
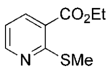
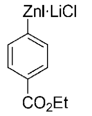
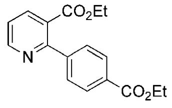
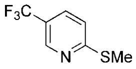
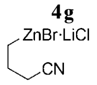
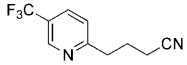
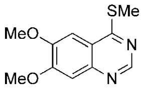
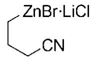
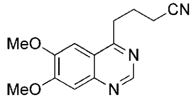
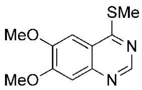
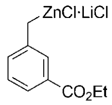
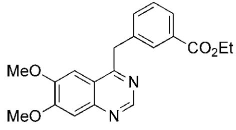
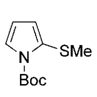
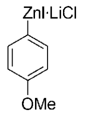
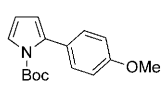
Thus, 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2a**, 1.0 equiv) reacted with 4-methoxyphenylzinc iodide (**4a**, 1.5 equiv) in THF (25 °C, 5 h) to provide the triazine **5a** in 83% yield (Table 1, entry 1). Furthermore, the triazine **2a** was used for a cross-coupling reaction with cyclohexylzinc bromide (**4b**) in THF (25 °C, 20 h), which led to the functionalized triazine **5b** in 43% yield (Table 1, entry 2). Moreover, 4-cyanophenylzinc iodide (**4c**) reacted smoothly with methylthio-substituted pyridazine **2e** to give the functionalized pyridazine **5c** in 76% yield (25 °C, 4 h, Table 1, entry 3). Functionalized benzylic zinc reagents reacted straightforwardly and the coupling of 3-cyanobenzylzinc chloride (**4d**) and pyridazine **2e** afforded the substituted diarylmethane **5d** in 71% yield (50 °C, 14 h, Table 1, entry 4). Other diaza heterocycles, such as 2-thiomethylpyrazine (**2f**) or 2-thiomethylpyrimidine (**2g**), also underwent smooth cross-coupling reactions. Thus, the reactions of 1-naphthylzinc iodide (**4e**) or 3-(trifluoromethyl)benzylzinc chloride (**4f**) with methylthio-substituted pyrazine **2f**, as well as pyrimidine **2g** led to the desired compounds **5e**–**5g** in yields of 59–83% within 16–20 h at 25 °C (Table 1, entries 5–7). Furthermore, thioether-substituted pyridines were also suitable coupling partners for the described reaction protocol. Thus, nicotinic ester **2h** underwent an efficient cross-coupling with the electron-poor arylzinc reagent **4g** to afford ethyl 2-[4-(ethoxycarbonyl)phenyl]nicotinate (**5h**) in 69% yield (25 °C, 6 h, Table 1, entry 8). Similarly, trifluoromethyl-substituted pyridine **2i** gave, after cross-coupling with 4-cyanopropylzinc bromide (**4h**, 25 °C, 16 h), the alkylated heterocycle **5i** in 84% yield (Table 1, entry 9). The reaction of 6,7-dimethoxy-4-(methylthio)quinazoline (**2j**) with the same alkylzinc reagent **4h** or with the ester-substituted benzylic zinc reagent **4i** yielded the functionalized quinazolines **5j** and **5k** in yields of 74 and 78%, respectively (Table 1, entries 10 and 11). Finally, this Pd-catalyzed cross-coupling reaction could also be performed with electron-rich N-heterocycles, such as the Boc-protected pyrrole **2k**. Reaction of the latter with 4-methoxyphenylzinc iodide (**4a**) smoothly afforded *tert*-butyl 2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (**5l**) in 67% yield (25 °C, 2 h, Table 1, entry 12).



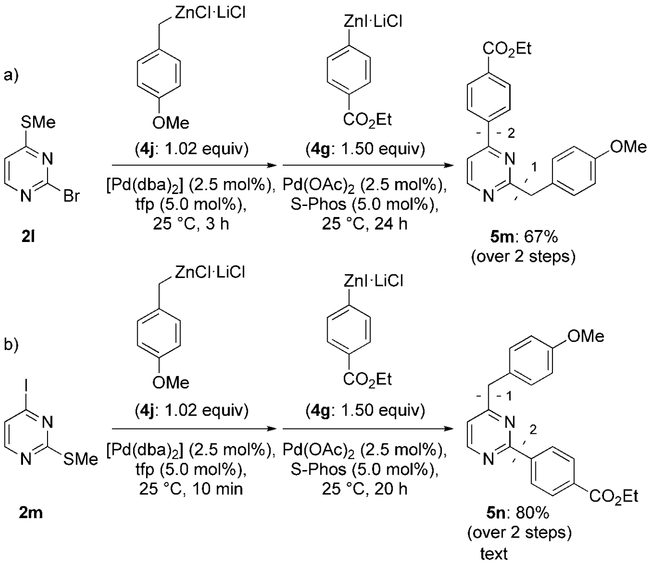
Scheme 2. Pd-catalyzed cross-coupling reaction of thiomethyl-substituted N-heterocycles **2** with functionalized organozinc reagents **4**; Cy = cyclohexyl.

Selective bis-functionalization of pyrimidines at their 2- and 4-positions could be achieved. Cross-coupling occurs at the 2- or 4-position depending on the substrate. Thus, the reaction of 2-bromo-4-(methylthio)pyrimidine (**2l**) with 4-methoxybenzylzinc chloride (**4j**, 1.02 equiv) proceeded rapidly in the presence of [Pd(dba)$_2$]/tfp (dba = dibenzylideneacetone, tfp = tri(2-furyl)phosphine) within 3 h at 25 °C (Scheme 3a).[17] After direct addition of a second catalyst system (Pd(OAc)$_2$/S-Phos) to the reaction mixture, a second cross-coupling occurred with 4-(ethoxycarbonyl)phenylzinc iodide (**4g**, 1.50 equiv) to provide the 2,4-disubstituted pyrimidine **5m** in 67% overall yield. Alternatively, 4-iodo-2-(methylthio)pyrimidine (**2m**) was converted into the regioisomeric 2,4-disubstituted pyrimidine **5n** by first performing

Table 1. Pd-catalyzed cross-coupling reactions of thiomethylated N-heterocycles.

| Entry | Electrophile | Zinc reagent | Product, Conditions, Yield[a] |
|---|---|---|---|
| 1 |  **2a** |  **4a** |  **5a**: 25 °C, 5 h, 83 % |
| 2 |  **2a** |  **4b** |  **5b**: 25 °C, 20 h, 43 % |
| 3 |  **2e** |  **4c** |  **5c**: 25 °C, 4 h, 76 % |
| 4 |  **2e** |  **4d** |  **5d**: 50 °C, 14 h, 71 % |
| 5 |  **2f** |  **4e** |  **5e**: 25 °C, 18 h, 83 % |
| 6 |  **2g** |  **4e** |  **5 f**: 25 °C, 20 h, 75 % |
| 7 |  **2g** |  **4 f** |  **5g**: 25 °C, 16 h, 59 % |
| 8 |  **2h** |  **4g** |  **5h**: 25 °C, 6 h, 69 % |
| 9 |  **2i** |  **4h** |  **5i**: 25 °C, 16 h, 84 % |
| 10 |  **2j** |  **4h** |  **5j**: 25 °C, 5 h, 74 % |
| 11 |  **2j** |  **4i** |  **5k**: 50 °C, 12 h, 78 % |
| 12 |  **2k** |  **4a** |  **5l**: 25 °C, 2 h, 67 % |

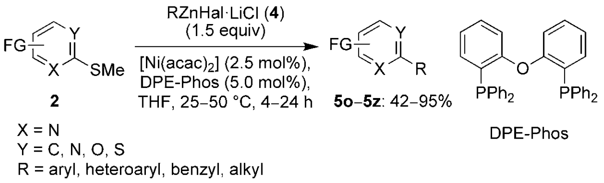
[a] Yield of isolated, analytically pure product.



Scheme 3. Selective one-pot cross-coupling reactions of a) 2-bromo-4-(methylthio)pyrimidine (**2l**) and b) 4-iodo-2-(methylthio)pyrimidine (**2m**).

a cross-coupling with 4-methoxybenzylzinc chloride (**4j**, 1.02 equiv) using [Pd(dba)$_2$]/tfp (25 °C, 10 min) and then carrying out a second cross-coupling with the arylzinc reagent **4g** (1.50 equiv) in the presence of Pd(OAc)$_2$/S-Phos (25 °C, 20 h). The pyrimidine **5n** was obtained in 80 % overall yield by this one-pot double cross-coupling sequence (Scheme 3b).

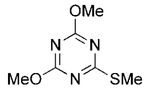
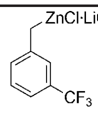
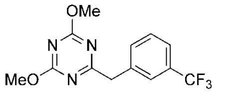
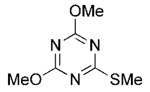
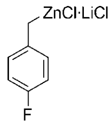
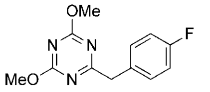
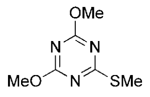
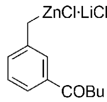
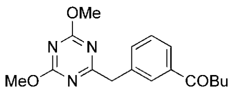
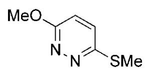
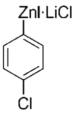
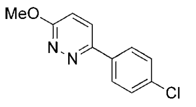
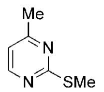
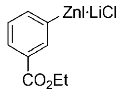
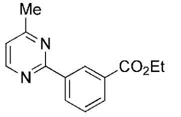
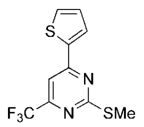
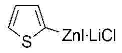
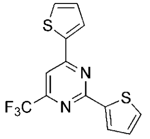
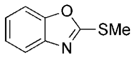
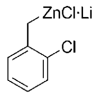
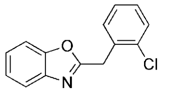
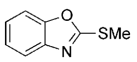
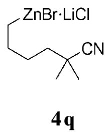
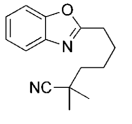
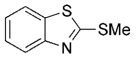
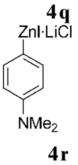
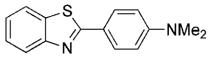
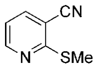
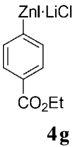
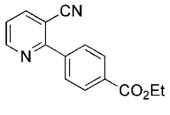
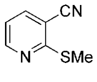
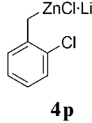
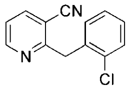
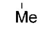
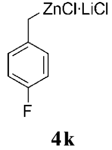
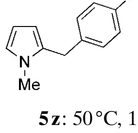
**Ni-catalyzed cross-coupling reactions of thiomethyl-substituted N-heterocycles with organozinc reagents**: Thiomethylated N-heterocycles (1.0 equiv) could also be cross-coupled with functionalized aryl-, benzylic-, and alkylzinc reagents (1.5 equiv) under Ni$^0$ catalysis. By using the inexpensive and robust system of [Ni(acac)$_2$] (2.5 mol %) and bis(2-diphenylphosphinophenyl)ether (DPE-Phos, 5.0 mol %), the reactions took place within 5–20 h at 25 °C in THF (Scheme 4).



Scheme 4. Ni-catalyzed cross-coupling reaction of thiomethyl-substituted N-heterocycles **2** with functionalized organozinc reagents **4**.

Utilizing this protocol, the triazine **2a** (1.0 equiv) underwent cross-coupling with the trifluoromethyl-substituted benzylic zinc reagent **4 f** (1.5 equiv) in 4 h at 25 °C, to afford 2,4-dimethoxy-6-[3-(trifluoromethyl)benzyl]-1,3,5-triazine (**5o**) in 72 % yield (Table 2, entry 1). Similarly, triazine **2a** reacted with 4-fluorobenzylzinc chloride (**4k**) or 3-penta-

Table 2. Ni-catalyzed cross-coupling reactions of thiomethylated N-heterocycles.

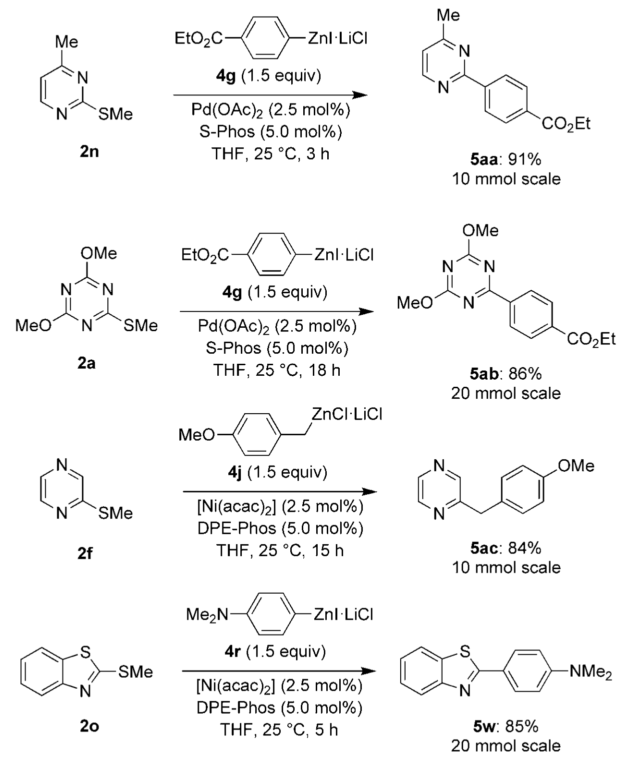
| Entry | Electrophile | Zinc reagent | Product, Conditions, Yield[a] |
|---|---|---|---|
| 1 |  **2a** |  **4f** |  **5o**: 25 °C, 4 h, 72 % |
| 2 |  **2a** |  **4k** |  **5p**: 25 °C, 4 h, 89 % |
| 3 |  **2a** |  **4l** |  **5q**: 25 °C, 5 h, 82 % |
| 4 |  **2e** |  **4m** |  **5r**: 25 °C, 6 h, 72 % |
| 5 |  **2n** |  **4n** |  **5s**: 25 °C, 12 h, 95 % |
| 6 |  **2d** |  **4o** |  **5t**: 25 °C, 16 h, 94 % |
| 7 |  **2c** |  **4p** |  **5u**: 25 °C, 18 h, 76 % |
| 8 |  **2c** |  **4q** |  **5v**: 25 °C, 12 h, 82 % |
| 9 |  **2o** |  **4r** |  **5w**: 25 °C, 5 h, 89 % |
| 10 |  **2p** |  **4g** |  **5x**: 25 °C, 18 h, 67 % |
| 11 |  **2p** |  **4p** |  **5y**: 25 °C, 24 h, 69 % |
| 12 |  **2b** |  **4k** |  **5z**: 50 °C, 18 h, 42 % |

[a] Yield of isolated, analytically pure product.

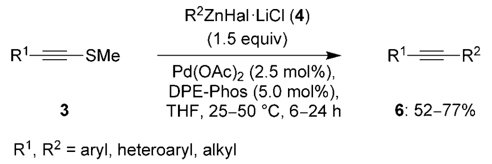
noylbenzylzinc chloride (**4l**) to give the diarylmethanes **5p** and **5q** in yields of 89 and 82 %, respectively (Table 2, entries 2 and 3). Thiomethyl-substituted pyridazine **2e** underwent a straightforward cross-coupling with 4-chlorophenylzinc iodide (**4m**) to afford the 3,6-difunctionalized pyridazine **5r** in 72 % yield (Table 2, entry 4). Cross-coupling of 4-methyl-2-(methylthio)pyrimidine (**2n**) with the electron-deficient ester-substituted arylzinc reagent **4n** provided the 2-arylpyrimidine **5s** in 95 % yield (Table 2, entry 5). The reaction of trifluoromethylated pyrimidine **2d** with 2-thienylzinc iodide (**4o**) gave the trisubstituted pyrimidine **5t** in 94 % yield (Table 2, entry 6). Alkylzinc reagents were also found to be well suited to these Ni-catalyzed reactions. Thus, as expected, reactions of 2-methylthiobenzoxazole (**2c**) with either the chloro-substituted benzylic zinc reagent **4p** or 5-cyano-5-methylhexylzinc bromide (**4q**) at 25 °C provided the benzoxazole derivatives **5u** and **5v** in yields of 76 and 82 %, respectively (Table 2, entries 7 and 8). Similarly, the cross-coupling reaction of 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**4r**) with benzo[*d*]thiazole **2o** gave the 2-arylbenzothiazole **5w** in 89 % yield (25 °C, 5 h, Table 2, entry 9). Furthermore, reactions of 2-(methylthio)nicotinonitrile (**2p**) with the organozinc reagents **4g** and **4p** led to the 2,3-disubstituted pyridines **5x** and **5y** in yields of 67 and 69 %, respectively (Table 2, entries 10 and 11). Finally, the electron-rich 1-methyl-2-(methylthio)-1*H*-pyrrole (**2b**) also reacted well with 4-fluorobenzylzinc chloride (**4k**) using [Ni(acac)$_2$]/DPE-Phos to afford the functionalized pyrrole **5z** in 42 % yield (50 °C, 18 h, Table 2, entry 12).

**Large-scale cross-coupling reactions of thiomethylated N-heterocycles**: To demonstrate that these cross-coupling protocols can be scaled-up, additional Pd- and Ni-catalyzed reactions were carried out on a larger scale. Thus, pyrimidine **2n** (1.0 equiv) was reacted with 4-(ethoxycarbonyl)phenylzinc iodide (**4g**, 1.5 equiv) on a 10 mmol scale under Pd catalysis (25 °C, 3 h), which gave ethyl 4-(4-methylpyrimidin-2-yl)benzoate (**5aa**) in 91 % yield (Scheme 5). This arylzinc iodide **4g** also underwent a straightforward cross-coupling reaction with 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2a**) on a 20 mmol scale, which gave the triazine **5ab** in 86 % yield (25 °C, 18 h). 2-Methylthiopyrazine (**2f**) was used in a Ni-catalyzed cross-coupling reaction with 4-methoxybenzylzinc chloride (**4j**), which led to the functionalized diarylmethane **5ac** (25 °C, 15 h, 10 mmol scale, 84 % yield). Finally, the arylzinc reagent **4r** reacted smoothly with the thiomethyl-substituted benzothiazole **2o** to give 4-(benzo[*d*]thiazol-2-yl)-*N*,*N*-dimethylaniline (**5w**) in 85 % yield (25 °C, 5 h, 20 mmol scale).

**Pd-catalyzed cross-coupling reactions of ethynyl thioethers**: Pd$^0$-catalyzed cross-coupling reactions of functionalized aryl-, heteroaryl-, and alkylzinc reagents (1.5 equiv) with various thiomethyl-substituted acetylenes (1.0 equiv) were achieved by using Pd(OAc)$_2$/DPE-Phos as the catalytic system (Scheme 6). These reactions could be carried out at 25–50 °C and were complete within 6–24 h.



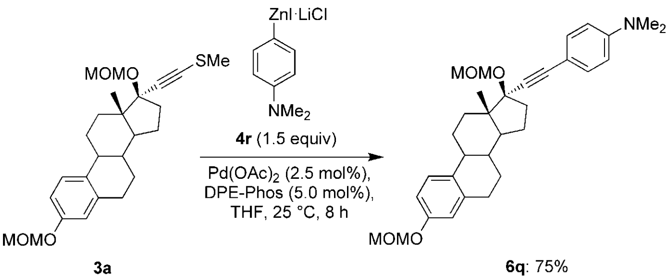
Scheme 5. Large-scale cross-couplings of thiomethyl-substituted N-heterocycles **2** with organozinc reagents **4** under Pd or Ni catalysis.



Scheme 6. Pd-catalyzed cross-coupling reaction of thiomethyl-substituted acetylenes **3** with functionalized organozinc reagents **4**.

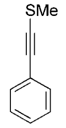
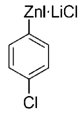
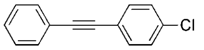
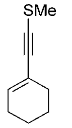
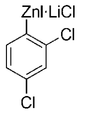
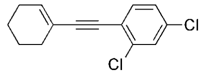
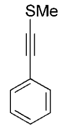
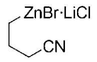
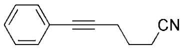
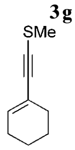
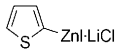
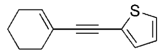
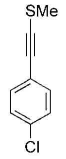
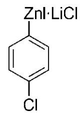
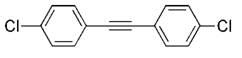
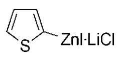
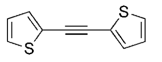
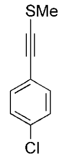
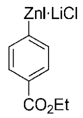
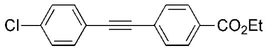
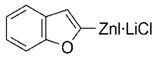
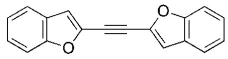
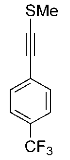
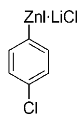
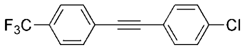
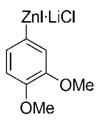
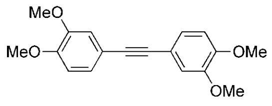
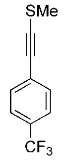
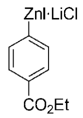
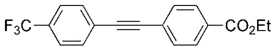
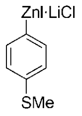
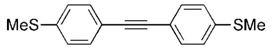
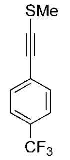
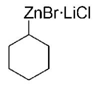
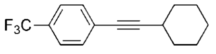
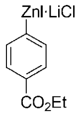
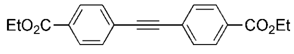
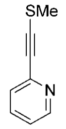
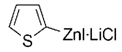
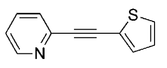
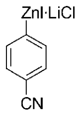
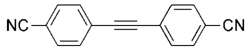
Thus, [(methylthio)ethynyl]benzene (**3c**, 1.0 equiv) reacted with 4-chlorophenylzinc iodide (**4m**, 1.5 equiv) to afford the bis-arylacetylene **6a** in 68 % yield (25 °C, 24 h, Table 3, entry 1). Acetylene **3c** was also used for cross-coupling reactions with functionalized alkylzinc reagents. For example, 4-cyanopropylzinc bromide (**4h**) underwent a smooth cross-coupling reaction with **3c** to afford alkyne **6b** in 52 % yield (50 °C, 16 h, Table 3, entry 2). Moreover, 1-chloro-4-[(methylthio)ethynyl]benzene (**3d**) reacted well with 4-chlorophenylzinc iodide (**4m**) to afford the symmetrically substituted bis-arylacetylene **6c** in 73 % yield (50 °C, 12 h, Table 3, entry 3). Sensitive functional groups, such as an ester group, were also tolerated in this cross-coupling reaction. Thus, reaction of the chloro-substituted phenylacetylene **3d** with 4-(ethoxycarbonyl)phenylzinc iodide (**4g**) provided the functionalized bis-arylacetylene **6d** in 53 % yield (50 °C, 6 h, Table 3, entry 4). Similarly, 1-trifluoromethyl-4-[(methylthio)ethynyl]benzene (**3e**) reacted smoothly with the electron-deficient zinc reagents **4m** and **4g** at 25 °C to give the expected products **6e** and **6f** in yields of 76 and 77 %, respectively (Table 3, entries 5 and 6). Secondary alkylzinc reagents could also be used. Cyclohexylzinc bromide (**4b**) underwent a smooth cross-coupling reaction with the unsaturated thioether **3e** (25 °C, 18 h), from which the substituted cyclohexylethylene derivative **6g** was isolated in 66 % yield (Table 3, entry 7). The use of heterocyclic reagents as both the electrophile and the organozinc species proved to be compatible with these reaction conditions. Thus, the pyridine derivative **3f** could be coupled with 2-thienylzinc iodide (**4o**) to give the bis-heteroarylacetylene **6h** in 72 % yield (50 °C, 8 h, Table 3, entry 8). Alkyl-substituted acetylenes have also been successfully used, and the cross-coupling reactions of 1-[(methylthio)ethynyl]cyclohexene (**3g**) with 2,4-dichlorophenylzinc iodide (**4s**) or 2-thienylzinc iodide (**4o**, 25 °C, 10–16 h) led to the expected cyclohexenylacetylenes **6i** and **6j** in yields of 69 and 65 %, respectively (Table 3, entries 9 and 10). Remarkably, bis(methylthio)acetylene (**3b**, 1.0 equiv) could be easily cross-coupled using the catalytic system and 3.0 equivalents of the organozinc compound. This is especially useful since the corresponding dihaloacetylenes are known to be toxic, carcinogenic, and explosive, and consequently not practical substrates. Thus, the thioether-substituted alkyne **3b** was functionalized with heteroarylzinc reagent **4o** or 2-benzofuranylzinc iodide (**4t**) to afford the symmetrically substituted acetylenes **6k** and **6l** in yields of 67 and 74 %, respectively (50 °C, 3–20 h, Table 3, entries 11 and 12). Electron-rich arylzinc reagents **4u** and **4v**, as well as their electron-deficient counterparts, such as 4-(ethoxycarbonyl)phenylzinc iodide (**4g**) and 4-cyanophenylzinc iodide (**4c**), each reacted smoothly with bis(methylthio)acetylene (**3b**) to deliver the bis-arylacetylenes **6m**–**6p** in yields of 64–79 % (25–50 °C, 10–16 h, Table 3, entries 13–16).

Finally, the (methylthio)ethynyl-substituted steroid **3a** was prepared starting from commercially available ethynyl estradiol (Scheme 1e) and was easily functionalized by using 4-(dimethylamino)phenylzinc iodide (**4r**, 1.5 equiv, 25 °C, 8 h) to afford the protected ethynyl estradiol derivative **6q** in 75 % yield (Scheme 7).



Scheme 7. Pd-catalyzed cross-coupling reaction of the MOM-protected ethynyl estradiol derivative **3a** with 4-(*N*,*N*-dimethylamino)phenylzinc iodide (**4r**).

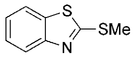
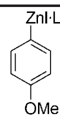
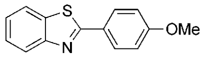
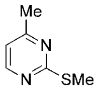
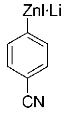
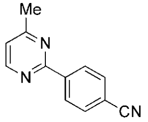
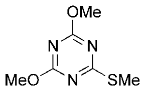
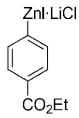
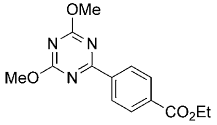
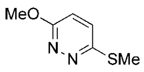
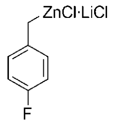
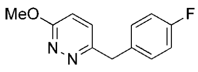
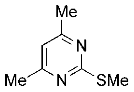
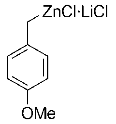
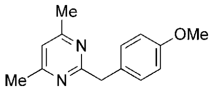
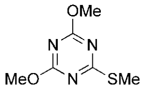
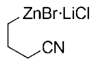
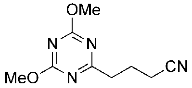
Table 3. Pd-catalyzed cross-coupling reactions of thiomethylated acetylenes.

| Entry | Electrophile | Zinc reagent | Product, Conditions, Yield[a] | Entry | Electrophile | Zinc reagent | Product, Conditions, Yield[a] |
|---|---|---|---|---|---|---|---|
| 1 | <br>**3c** | <br>**4m** | <br>**6a**: 25 °C, 24 h, 68 % | 9 | <br>**3g** | <br>**4s** | <br>**6i**: 25 °C, 10 h, 69 % |
| 2 | <br>**3c** | <br>**4h** | <br>**6b**: 50 °C, 16 h, 52 % | 10 | <br>**3g** | <br>**4o** | <br>**6j**: 25 °C, 16 h, 65 % |
| 3 | <br>**3d** | <br>**4m** | <br>**6c**: 50 °C, 12 h, 73 % | 11 | <br>**3b** | <br>**4o** | <br>**6k**: 50 °C, 20 h, 67 %[b] |
| 4 | <br>**3d** | <br>**4g** | <br>**6d**: 50 °C, 6 h, 53 % | 12 | <br>**3b** | <br>**4t** | <br>**6l**: 50 °C, 3 h, 74 %[b] |
| 5 | <br>**3e** | <br>**4m** | <br>**6e**: 25 °C, 12 h, 76 % | 13 | <br>**3b** | <br>**4u** | <br>**6m**: 25 °C, 10 h, 79 %[b] |
| 6 | <br>**3e** | <br>**4g** | <br>**6f**: 25 °C, 20 h, 77 % | 14 | <br>**3b** | <br>**4v** | <br>**6n**: 25 °C, 14 h, 73 %[b] |
| 7 | <br>**3e** | <br>**4b** | <br>**6g**: 25 °C, 18 h, 66 % | 15 | <br>**3b** | <br>**4g** | <br>**6o**: 50 °C, 12 h, 67 %[b] |
| 8 | <br>**3f** | <br>**4o** | <br>**6h**: 50 °C, 8 h, 72 % | 16 | <br>**3b** | <br>**4c** | <br>**6p**: 50 °C, 16 h, 64 %[b] |

[a] Yield of isolated, analytically pure product. [b] 3.0 equivalents of the zinc reagent were used.

**Comparison between Pd and Ni catalysts used in cross-coupling reactions of organozinc reagents with N-heterocyclic methyl thioethers**: We have compared the reactivities of the two different catalytic systems used for the cross-coupling reactions between various functionalized zinc reagents (1.5 equiv) and thiomethyl-substituted N-heterocycles (1.0 equiv). Six different compounds were prepared using both of the described protocols. The reaction times, temperatures, and yields of the isolated products were compared, and the results of these experiments are shown in Table 4. Arylzinc reagents were investigated first. Thus, the electron-rich organozinc reagent **4a** (1.5 equiv) was treated with 2-thiomethylbenzothiazole **2o** (1.0 equiv) with $Pd(OAc)_2$/S-Phos or $[Ni(acac)_2]$/DPE-Phos (2.5 mol %/5 mol %). Full

Table 4. Comparison of Pd- and Ni-catalyzed cross-coupling reactions of thiomethylated N-heterocycles with organozinc reagents.

| Entry | Thioether | Zinc reagent | Product, Conditions, Yield[a] |
|---|---|---|---|
| 1 |  **2o** |  **4a** |  **7a**: Pd: 25 °C, 2 h, 73 %; Ni: 25 °C, 3 h, 85 % |
| 2 |  **2n** |  **4c** |  **7b**: Pd: 25 °C, 16 h, 74 %; Ni: 25 °C, 18 h, 73 % |
| 3 |  **2a** |  **4g** |  **5ab**: Pd: 25 °C, 5 h, 84 %; Ni: 25 °C, 7 h, 81 % |
| 4 |  **2e** |  **4k** |  **7c**: Pd: 25 °C, 5 h, 73 %; Ni: 25 °C, 5 h, 74 % |
| 5 |  **2q** |  **4j** |  **7d**: Pd: 50 °C, 8 h, 94 %; Ni: 25 °C, 3 h, 85 % |
| 6 |  **2a** |  **4h** |  **7e**: Pd: 25 °C, 5 h, 66 %; Ni: 25 °C, 48 h, 68 % |

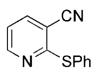
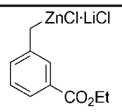
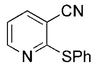
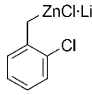
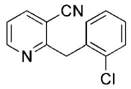
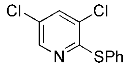
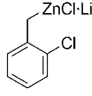
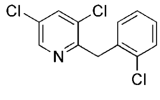
[a] Yield of isolated, analytically pure product.

conversion was achieved with the Pd catalyst after 2 h at 25 °C, giving the product in 73 % yield, whereas by using the Ni catalyst, the reaction took place within 3 h, delivering the cross-coupled product **7a** in 85 % yield (Table 4, entry 1). Electron-deficient 4-cyanophenylzinc iodide (**4c**) reacted with pyrimidine **2n** at 25 °C in the presence of either catalytic system in 16–18 h to give 2-arylpyrimidine **7b** in comparable yields (73 and 74 %, Table 4, entry 2). Also, the reaction of triazine **2a** and 4-(ethoxycarbonyl)phenylzinc iodide (**4g**) led to the trisubstituted triazine **5ab** after similar reaction times at 25 °C and in similar yields (Pd: 5 h, 84 % yield; Ni: 7 h, 81 % yield, Table 4, entry 3). The reaction behavior of benzylic zinc reagents was also investigated. Whereas the cross-coupling of electron-deficient 4-fluorobenzylzinc chloride (**4k**) with pyridazine **2e** to afford heterocycle **7c** gave similar results using both catalytic systems (25 °C, 5 h, 73 and 74 % yields, Table 4, entry 4), electron-rich reagents showed different activity. 4,6-Dimethyl-2-methylthiopyrimidine (**2q**) could only be functionalized with 4-methoxybenzylzinc chloride (**4j**) utilizing the $Pd(OAc)_2$/S-Phos system in 8 h at 50 °C, whereby the diarylmethane **7d** was obtained in 94 % yield. When the same reaction was performed with $[Ni(acac)_2]$/DPE-Phos as the catalytic system, full conversion of the pyrimidine **2q** was observed after just 3 h at 25 °C, although the yield of **7d** was lower at 85 % (Table 4, entry 5). Furthermore, alkylzinc reagents were also studied, which showed different reactivities with the respective catalysts. Thus, triazine **2a** underwent a smooth cross-coupling reaction with 4-cyanopropylzinc bromide (**4h**) (25 °C, 5 h, 66 % yield) in the presence of $Pd(OAc)_2$, but by using $[Ni(acac)_2]$ it took 48 h at 25 °C to deliver a slightly higher yield of alkyltriazine **7e** (68 %, Table 4, entry 6).

Thus, the two catalytic systems used here, $Pd(OAc)_2$/S-Phos and $[Ni(acac)_2]$/DPE-Phos, perform equally well for most substrates. Although the Ni-catalyzed reactions usually require longer reaction times, especially for alkylzinc reagents, the yields of the isolated products are very close to those achieved under Pd catalysis. An advantage of the $[Ni(acac)_2]$ system is that full conversions of all electrophiles are obtained at just 25 °C, whereas in some cases the $Pd(OAc)_2$ system requires elevated temperatures (50 °C).

**Cross-coupling reactions of thiophenylated N-heterocycles**: Despite the thiomethyl moiety being the most economic thioester leaving group in the cross-coupling reactions, the advantages of these methods were further stressed by employing thiophenylated N-heterocycles. These could easily be prepared by nucleophilic attack of thiophenolate on heterocyclic chlorides in analogy to Scheme 1a. The reaction of 2-(phenylthio)nicotinonitrile (**2r**, 1.0 equiv) with 3-(ethoxycarbonyl)benzylzinc chloride (**4i**, 1.5 equiv) using $Pd(OAc)_2$ and S-Phos (2.5 mol %/5.0 mol %) provided the substituted pyridine **7f** in 91 % yield after 8 h at 25 °C (Table 5, entry 1). The same pyridine **2r** underwent a smooth cross-coupling reaction with *ortho*-functionalized benzylzinc reagent **4p** and the functionalized nicotinonitrile **5y** was isolated in 87 % yield (25 °C, 14 h, entry 2). 3-Chlorobenzylzinc

Table 5. Pd-catalyzed cross-coupling reactions of thiophenylated N-heterocycles.

| Entry | Electrophile | Zinc reagent | Product, Conditions, Yield[a] |
|---|---|---|---|
| 1 |  **2r** |  **4i** |  **7f**: 25 °C, 8 h, 91 % |
| 2 |  **2r** |  **4p** |  **5y**: 25 °C, 14 h, 87 % |
| 3 |  **2s** |  **4p** |  **7g**: 25 °C, 16 h, 68 % |

[a] Yield of isolated, analytically pure product.

chloride (**4p**) could also be cross-coupled with phenylthioether **2s** to afford the trichloro-substituted bis-arylmethane **7g** in 68 % yield (25 °C, 16 h, Table 5, entry 3). These examples demonstrate the versatility of these reaction protocols and the scope of thioethers that are compatible with them.

## Conclusion

We have developed two different, very efficient catalytic systems, $Pd(OAc)_2$/S-Phos and $[Ni(acac)_2]$/DPE-Phos, for the cross-coupling of a range of thiomethylated N-heterocycles with functionalized organozinc reagents. Aryl-, benzylic, as well as alkylzinc halides, with sensitive functional groups, such as ester, nitrile, or ketone, can be used, and all of the Ni-catalyzed, as well as most of the Pd-catalyzed reactions can be conducted at 25 °C. No copper(I) salts are necessary to achieve good yields of the cross-coupling products and these protocols are suitable for multigram reactions. A third catalytic system ($Pd(OAc)_2$/DPE-Phos) has been used for thiomethylated alkynes, as well as bis(thiomethyl)acetylene. In a series of comparison experiments, the different activities of the catalysts towards different combinations of heterocycles and organometallic reagents have been evaluated. The possibility of using different classes of thioethers as electrophiles has been demonstrated, along with the different synthetic approaches for their preparation. Further extensions of this methodology, as well as applications in natural product synthesis and materials chemistry, are currently underway in our laboratories.

## Experimental Section

For experimental procedures, analytical data, and NMR spectra, see the Supporting Information.

**Representative preparation of 5q**: In a dry, argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, compound **2a** (187 mg, 1.00 mmol), $[Ni(acac)_2]$ (6.4 mg, 2.5 mol %), and DPE-Phos (27 mg, 5.0 mol %) were dissolved in THF (1 mL). After 10 min of stirring, a solution of (3-pentanoyl)benzylzinc chloride (**4l**) in THF (0.44 M, 3.41 mL, 1.50 mmol) was added dropwise, and the reaction mixture was stirred for 5 h at 25 °C until GC analysis of a hydrolyzed aliquot showed full conversion of the electrophile. The reaction mixture was then quenched with a saturated aqueous solution of $K_2CO_3$ (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($Na_2SO_4$), and the solvent was removed in vacuo. Purification by flash chromatography (silica gel; pentane/$Et_2O$, 1:1) afforded the triazine **5q** (258 mg, 82 %) as a clear oil. $^1$H NMR ($CDCl_3$, 600 MHz): $\delta=7.96$–7.95 (m, 1 H), 7.83–7.79 (m, 1 H), 7.58–7.54 (m, 1 H), 7.50–7.35 (m, 1 H), 4.06 (s, 2 H), 3.99 (s, 6 H), 2.93 (t, $J=7.43$ Hz, 2 H), 1.73–1.63 (m, 2 H), 1.44–1.32 (m, 2 H), 0.92 ppm (t, $J=7.31$ Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta=200.3$, 180.9, 172.5, 137.3, 136.9, 133.9, 129.0, 128.7, 126.7, 55.1, 44.9, 38.4, 26.4, 22.4, 13.9 ppm; IR (ATR): $\tilde{\nu}=2955$ (w), 1682 (m), 1546 (vs), 1500 (s), 1458 (m), 1378 (m), 1350 (vs), 1264 (m), 1231 (m), 1202 (m), 1106 (m), 1091 (m), 1069 (m), 820 (m), 731 (m), 690 cm$^{-1}$ (m); MS (EI, 70 eV): $m/z$ (%): 316 (4), 315 ($M^+$, 15), 274 (7), 273 (40), 259 (15), 258 (100), 245 (6), 231 (11), 230 (4), 158 (6); HRMS (EI): $m/z$: calcd for $C_{17}H_{21}N_3O_3$: 315.1583; found: 315.1577.

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[17] This catalytic system proved to be the best for achieving a selective coupling with the carbon–halogen bonds of pyrimidines **2l** and **2m**. When using Pd(OAc)$_2$/S-Phos for the first step of Scheme 3, a mixture of the two possible cross-coupling products was obtained.

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