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Pd-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles

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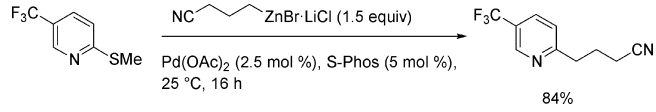
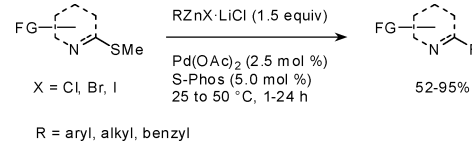
ABSTRACT



Various thiomethyl-substituted *N*-heterocycles (pyridines, pyrimidines, pyrazines, pyridazines, triazines, benzothiazoles, benzoxazoles, pyrazoles, benzindazoles, quinazolines, etc.) undergo smooth Pd-catalyzed cross-coupling reactions with functionalized aryl-, heteroaryl-, benzylic-, and alkylzinc reagents using $Pd(OAc)_2$/S-Phos as the catalytic system mostly at 25 °C. No copper salt is required to perform these reactions.

The transition-metal catalyzed cross-coupling reaction of unsaturated thioethers with Grignard reagents has been pioneered by Wenkert in 1979.[1] It represents an attractive method for converting a C−S bond into a C−C bond. More recently, Liebeskind and Srogl have shown that various boronic acids[2] as well as organotin,[3] organozinc,[4] and organoindium reagents[5] undergo efficient cross-couplings with thioethers or -esters using a Pd- or Ni-catalysis. Casalnuovo showed also that benzylzinc bromide reacts with heterocyclic thioethers in the presence of $Pd(PPh_3)_4$ at elevated temperatures.[6] Strambuli used such Ni- and Pd-catalyzed cross-couplings for the functionalization of oxazoles.[7] A mild iron-catalyzed cross-coupling of alkenyl sulfides with Grignard reagents has also been described by Yoshida.[8] Functionalized organozinc reagents are now readily available.[9] Herein, we report an efficient Pd(0)-catalyzed cross-coupling reaction of functionalized aryl-, benzylic-, and alkylzinc reagents with various thiomethyl-substituted *N*-heterocycles using $Pd(OAc)_2$/S-Phos as the catalytic system which has been introduced by Buchwald (Scheme 1).[10,11]

Scheme 1. Pd-Catalyzed Cross-Coupling Reaction of Thiomethyl-Substituted *N*-Heterocycles with Various Organozinc Reagents



Thus, the reaction of 4-methoxyphenylzinc iodide (**1a**) with 2-(methylthio)-5-(trifluoromethyl)pyridine (**2a**) provided

(1) (a) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637. (b) Wenkert, E.; Ferreira, T. W. *J. Chem. Soc., Chem. Commun.* **1982**, 840. (c) Wenkert, E.; Shepard, M. E.; McPhail, A. T. *J. Chem. Soc., Chem. Commun.* **1986**, 1390.

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(3) (a) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (b) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033.

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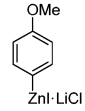
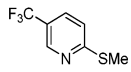
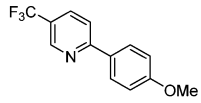
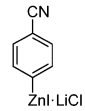
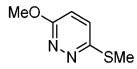
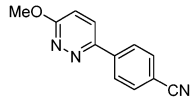
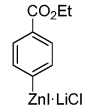
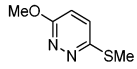
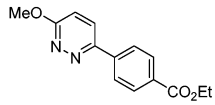
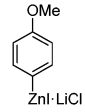
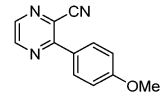
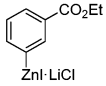
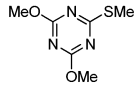
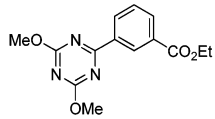
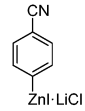
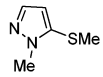
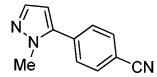
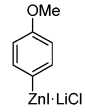
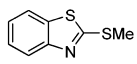
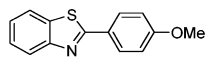
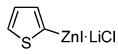
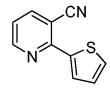
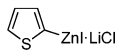
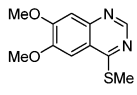
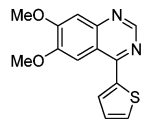
Table 1. Reaction of Aromatic and Heteroaromatic Zinc Reagents (**1**) with Thiomethyl-Substituted Heterocycles (**2**)

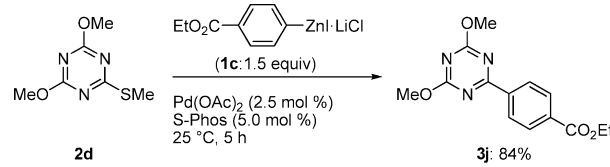
entry	arylzinc reagent (**1**)	electrophile (**2**)	product (**3**)	yield (%)[a]
1	 **1a**	 **2a**	 **3a**	95
2	 **1b**	 **2b**	 **3b**	76
3	 **1c**	 **2b**	 **3c**	77
4	 **1a**	 **2c**	 **3d**	57
5	 **1d**	 **2d**	 **3e**	84
6	 **1b**	 **2e**	 **3f**	52[b]
7	 **1a**	 **2f**	 **3g**	73
8	 **1e**	 **2g**	 **3h**	93
9	 **1e**	 **2h**	 **3i**	95

[a] Yield of analytically pure product. [b] Reaction performed at 50 °C.

the cross-coupling product **3a** in 95% yield (entry 1 of Table 1). Electron-poor zinc reagents **1b**,**c** bearing a nitrile or an ester function readily reacted with 3-methoxy-(6-methylthio)pyridazine (**2b**) leading to the functionalized pyridazines **3b**,**c** in 76−77% yield (entries 2 and 3). Cyano-substituted pyrazine **2c** is smoothly converted to the substituted pyrazine **3d** in 57% yield (entry 4). Furthermore, electron-rich triazines undergo the cross-coupling as well. Thus, dimethoxy-substituted triazine **2d** reacted with 3-ethoxycarbonylphenylzinc iodide (**1d**) furnishing the triazine **3e** in 84% yield (entry 5). Five-membered heterocycles such as pyrazole **2e** and condensed rings such as benzothiazole **2f** led to the expected products **3f**,**g** in 52−73% yield (entries 6 and 7). Moreover, heterocyclic zinc reagents readily participate to the cross-coupling under these conditions. Thus, 2-thienylzinc iodide (**1e**) reacted with the substituted pyridine **2g** and the quinazoline **2h** leading to the heterocyclic biphenyls **3h**,**i** in 93−95% yields (entries 8 and 9).

Using this method, it was possible to prepare the anti-inflammatory agent[12] **3j** in 84% yield by treating the 2,4,6-substituted triazine **2d** with the arylzinc reagent **1c** (Scheme 2). Furthermore, this Pd-catalyzed cross-coupling reaction

Scheme 2. Preparation of the Anti-Inflammatory Agent **3j**

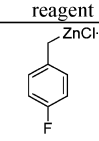
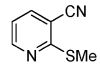
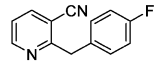
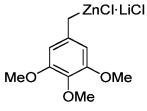
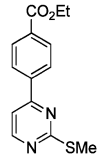
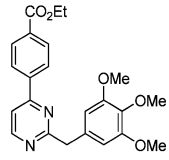
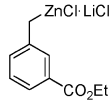
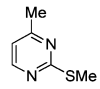
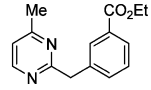
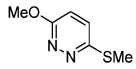
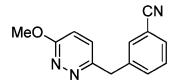
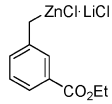
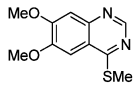
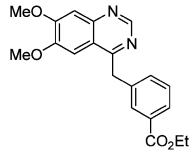
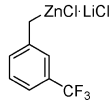
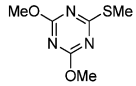
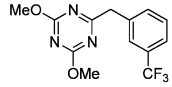
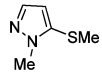
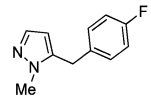
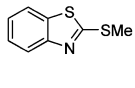
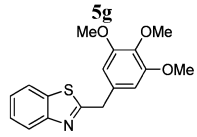
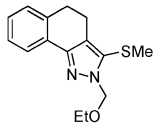
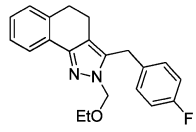


proceeds also well with benzylic zinc reagents of type **4**. Thus, the reaction of 4-fluorobenzylzinc chloride (**4a**) with the cyano-substituted pyridine **2g** provided the pyridine **5a** in 83% yield (entry 1 of Table 2). Ester-substituted pyrimidine **2i** underwent smooth cross-coupling with the 3,4,5-trimethoxy-substituted benzylic zinc reagent **4b** affording the 2-benzylated pyridine **5b** in 88% yield (entry 2). Functionalized pyrimidine **2j**, pyridazine **2b**, and quinazoline **2h** undergo also an efficient cross-coupling with various benzylic zinc reagents bearing an ester or a nitrile group furnishing the heterocyclic diarylmethanes **5c**−**e** in 71−78% yields (entries 3−5). Similarly, triazine **2d** reacted with 3-(trifluoromethyl)benzylzinc chloride (**4e**) leading to the triazine **5f** in 70% yield (entry 6). Moreover, thiomethyl-substituted five-membered rings **2e**−**k** underwent cross-couplings with benzylic zinc reagents **4a**,**b** furnishing the heterocycles **5g**−**i** in 62−80% yield (entries 7−9).

A selective bis-functionalization of pyrimidines in positions 2 and 4 can be achieved. Cross-coupling occurs first

(6) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, 905.
(7) Lee, K.; Counceller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, *11*, 1457.
(8) Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J.-i. *Org. Lett.* **2005**, *7*, 1219.
(9) (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040. (b) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107.
(10) (a) Altman, R. A.; Buchwald, S. L. *Nat. Protoc.* **2007**, *2*, 3115. (b) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096. (c) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
(11) $Pd(OAc)_2$/S-Phos was superior related to *i*Pr-PEPPSI, $Pd(dba)_2$/tfp, and $Pd(dppe)Cl_2$. In the absence of the Pd catalyst, no reaction occurs.
(12) (a) Menicagli, R.; Samaritani, S.; Signore, G.; Vaglini, F.; Dalla Via, L. *J. Med. Chem.* **2004**, *47*, 4649. (b) Dianzani, C.; Collino, M.; Gallicchio, M.; Samaritani, S.; Signore, G.; Menicagli, R.; Fantozzi, R. *J. Pharm. Pharmacol.* **2006**, *58*, 219. (c) Samaritani, S.; Signore, G.; Malanga, C.; Menicagli, R. *Tetrahedron* **2005**, *61*, 4475.

Table 2. Reaction of Benzylic Zinc Chlorides (**4**) with Thiomethyl-Substituted Heterocycles (**2**)

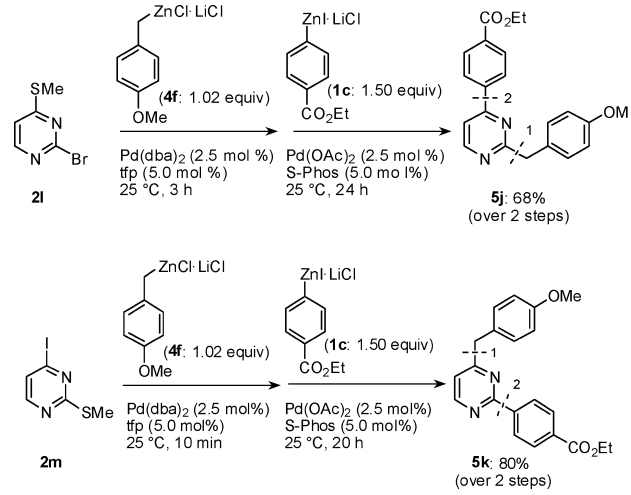
entry	benzylic zinc reagent (**4**)	electrophile (**2**)	product (**5**)	yield (%)[a]
1	 **4a**	 **2g**	 **5a**	83
2	 **4b**	 **2i**	 **5b**	88
3	 **4c**	 **2j**	 **5c**	73
4	 **4d**	 **2b**	 **5d**	71[b]
5	 **4c**	 **2h**	 **5e**	78[b]
6	 **4e**	 **2d**	 **5f**	70
7	 **4a**	 **2e**	 **5g**	80[b]
8	 **4b**	 **2f**	 **5h**	70
9	 **4a**	 **2k**	 **5i**	62[b]

[a] Yield of analytically pure product. [b] Reaction performed at 50 °C.

in position 2 or 4 depending on the substrate. Thus, the reaction of 2-bromo-4-(methylthio)pyrimidine[13] (**2l**) with 4-methoxybenzylzinc chloride (**4f**) proceeds rapidly in the presence of $Pd(dba)_2$/tfp (25 °C, 3 h). After a direct addition

(13) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.

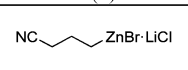
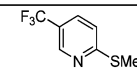
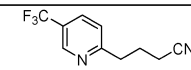
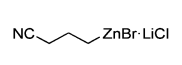
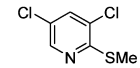
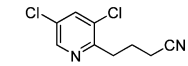
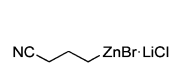
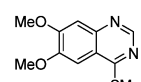
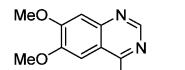
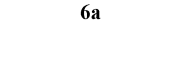
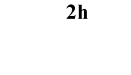
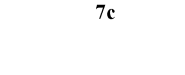
Scheme 3. Selective One-Pot Cross-Coupling Reactions of 2-Bromo-4-(methylthio)pyrimidine (**2l**) or 4-Iodo-2-(methylthio)pyrimidine (**2m**) Using $Pd(dba)_2$/tfp and in Situ $Pd(OAc)_2$/S-Phos



of a second catalyst system ($Pd(OAc)_2$/S-Phos) to the reaction mixture, a second cross-coupling occurs with (4-ethoxycarbonyl)phenylzinc iodide (**1c**) providing the 2,4-disubstituted pyrimidine **5j** in 68% overall yield (Scheme 3).

Alternatively, 4-iodo-2-(methylthio)pyrimidine[14] (**2m**) can be converted into the regiomeric 2,4-disubstituted pyrimidine **5k** by performing first a cross-coupling with 4-methoxyben-

Table 3. Reaction of Alkylzinc Reagents (**6**) with Thiomethyl-Substituted Heterocycles (**2**)

entry	alkylzinc reagent (**6**)	electrophile (**2**)	product (**7**)	yield (%)[a]
1	 **6a**	 **2a**	 **7a**	84
2	 **6a**	 **2n**	 **7b**	54
3	 **6a**	 **2h**	 **7c**	74
4	 **6a**	 **2d**	 **7d**	66
5	**6b**	**2e**	**7e**	69[b]

[a] Yield of analytically pure product. [b] Reaction performed at 50 °C.

zylzinc chloride (**4f**) using $Pd(dba)_2$/tfp (25 °C, 10 min) followed by a second cross-coupling with the arylzinc reagent **1c** in the presence of $Pd(OAc)_2$/S-Phos (25 °C, 20 h). The pyrimidine **5k** is obtained in 80% overall yield in this one-pot double cross-coupling sequence. The scope of this Pd-catalyzed cross-coupling reaction was extended to alkylzinc reagents. Thus, 4-cyanopropylzinc bromide (**6a**) reacted with trifluoromethyl-substituted pyridine **2a** providing the pyridine **7a** in 84% yield (entry 1 of Table 3).[15] Smooth cross-coupling occurred between alkylzinc reagent **6a** and pyridine **2n** providing the pyridine **7b** in 54% yield (entry 2). Moreover, thiomethyl-substituted quinazoline **2h** and triazine **2d** were converted to the desired products **7c**,**d** under standard conditions (66−74% yield; entries 3 and 4).

Finally, the pyrazole **2e** was reacted with 4-ethoxy-4-oxybutylzinc bromide (**6b**)leading to the functionalized pyrazole **7e** in 69% yield (entry 5).

In summary, we have reported a new Pd-catalyzed cross-coupling reaction using $Pd(OAc)_2$/S-Phos which proceeds mostly at room temperature. A broad range of functional groups are tolerated in this cross-coupling in which alkyl-, aryl-, heteroaryl, and benzylic zinc reagents can be used. Further extensions of this cross-coupling are currently underway in our laboratories.

(14) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993.

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

OL9017003

(15) Typical procedure: Preparation of 4-[5-(trifluoromethyl)pyridin-2-yl]butanenitrile (**7a**): In a dry and argon flushed Schlenk flask, equipped with a magnetic stirring bar and a rubber septum, 2-(methylthio)-5-(trifluoromethyl)pyridine (**2a**, 193 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 25 μmol), and S-Phos (20.5 mg, 50 μmol) were dissolved in dry THF (1 mL). After 10 min of stirring at 25 °C, (3-cyanopropyl)zinc bromide (**6a**, 3.66 mL, 1.5 mmol, 0.41 M in THF) was added dropwise. After 16 h at 25 °C, GC analysis of a hydrolyzed aliquot showed full conversion. The reaction mixture was quenched with sat. Na_2CO_3 solution (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, and after filtration the solvents were removed in vacuo. Flash column chromatography (pentane/Et_2O = 1:1 + 2-Vol% NEt_3) furnished the pyridine **7a** as a yellow oil (180 mg, 0.84 mmol, 84%).