

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

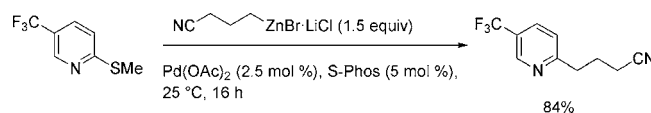
Albrecht Metzger, Laurin Melzig, Christina Despotopoulou, and Paul Knochel*

Department Chemie und Biochemie, Ludwig-Maximilians-University,
Butenandtstr. 5-13, 81377, Munich, Germany

paul.knochel@cup.uni-muenchen.de

Received July 24, 2009

ABSTRACT

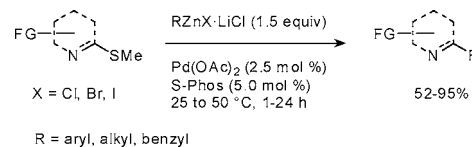


Various thiomethyl-substituted *N*-heterocycles (pyridines, pyrimidines, pyrazines, pyridazines, triazines, benzothiazoles, benzoxazoles, pyrazoles, benzindazoles, quinazolines, etc.) undergo smooth Pd-catalyzed cross-coupling reactions with functionalized aryl-, heteroaryl-, benzylic-, and alkylzinc 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 acids² as well as organotin,³ organozinc,⁴ and organoindium reagents⁵ 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(PPh₃)₄ at ele-

vated 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.

(2) (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, 2, 3229. (b) Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, 4, 979. (c) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, 4, 983. (d) Kusturin, C.; Liebeskind, L. S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* **2003**, 5, 4349. (e) Lengar, A.; Kappe, C. O. *Org. Lett.* **2004**, 6, 771.

(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.

(4) (a) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, 121, 9449. (b) For Pd-catalyzed reaction of organozinc reagents with thioimides see: (i) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, 67, 9304. (ii) Roberts, W. P.; Ghosh, I.; Jacobi, P. A. *Can. J. Chem.* **2004**, 82, 279.

(5) Fausett, B. W.; Liebeskind, L. S. *J. Org. Chem.* **2005**, 70, 4851.

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

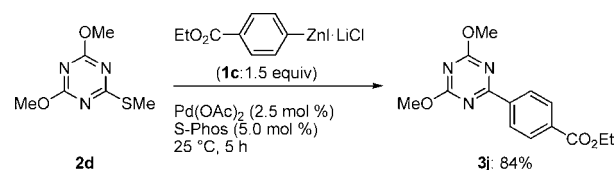
entry	arylzinc reagent (1)	electrophile (2)	product (3)	yield (%) ^a
1				95
2				76
3				77
4				57
5				84
6				52 ^b
7				73
8				93
9				95

^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 agent¹² **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

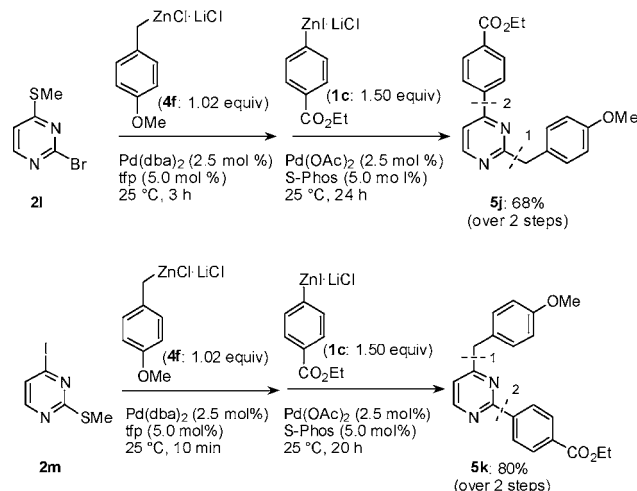
- (6) Angioletti, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, 905.
- (7) Lee, K.; Counceller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, *11*, 1457.
- (8) Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J.-i. *Org. Lett.* **2005**, *7*, 1219.
- (9) (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, 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 iPr-PEPPSI, Pd(dba)₂/tfp, and Pd(dppe)Cl₂. 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) ZnCl ₂ ·LiCl	electrophile (2)	product (5)	yield (%) ^a
1				83
2				88
3				73
4				71 ^b
5				78 ^b
6				70
7				80 ^b
8				70
9				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)pyrimidine¹³ (**2l**) with 4-methoxybenzylzinc chloride (**4f**) proceeds rapidly in the presence of Pd(dba)₂/tfp (25 °C, 3 h). After a direct addition

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)pyrimidine¹⁴ (**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				84
2				54
3				74
4				66
5				69 ^b

^a Yield of analytically pure product. ^b Reaction performed at 50 °C.(13) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.

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.

Acknowledgment. We thank the DFG and the European Research Council (ERC) for financial support. We thank Chemetall GmbH (Frankfurt), Evonik Industries AG (Hanau), and BASF SE (Ludwigshafen) for the generous gift of chemicals.

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. Na₂CO₃ solution (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na₂SO₄, and after filtration the solvents were removed in vacuo. Flash column chromatography (pentane/Et₂O = 1:1 + 2-Vol% NEt₃) furnished the pyridine **7a** as a yellow oil (180 mg, 0.84 mmol, 84%).