

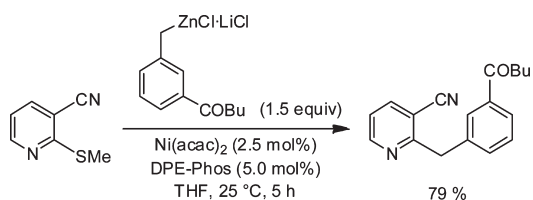
Room Temperature Cross-Coupling of Highly Functionalized Organozinc Reagents with Thiomethylated *N*-Heterocycles by Nickel Catalysis

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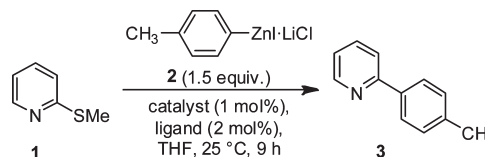
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A variety of thiomethyl-substituted *N*-heterocycles such as pyridines, isoquinolines, pyrimidines, pyrazines, pyridazines, quinazolines, triazines, benzothiazoles, or benzoxazoles undergo smooth Ni-catalyzed cross-coupling reactions with functionalized aryl-, heteroaryl-, alkyl-, and benzylic zinc reagents using an inexpensive Ni(acac)₂/DPE-Phos catalytic system at 25 °C.

The first cross-coupling reactions of thioethers with Grignard reagents, catalyzed by transition metals, were independently reported by Takei and Wenkert in 1979.¹ This method allows direct conversion of a carbon–sulfur bond into a carbon–carbon bond. Liebeskind described a Ni-catalyzed cross-coupling reaction using various sulfur functionalities as leaving groups.² Stambuli has prepared functionalized oxazoles with a Ni cross-coupling at higher temperatures.³ Recently, we have reported that thiomethyl-substituted heterocycles undergo efficient cross-couplings with various zinc reagents using the Pd(OAc)₂/S-Phos catalytic system.⁴ Although some progress has been reported,^{5,6} an improvement of the functional group tolerance and a lowering of the catalyst system cost would still be desirable. Organozinc reagents bearing sensitive functional

TABLE 1. Catalyst and Ligand Screening in the Cross-Coupling Reaction of 2-Thiomethylpyridine (1) with 4-Methylphenylzinc Iodide (2)

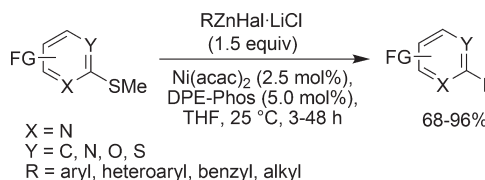


entry	metal	ligand	yield (%) ^a
1	Ni(PPh ₃) ₂ Br ₂		14
2	NiCl ₂ ·DME	H ₃ CC(CH ₂ PPh ₂) ₃	16
3	Ni(acac) ₂	IMes·HCl	16
4	Ni(acac) ₂	P(<i>o</i> -Tol) ₃	18
5	Ni(acac) ₂	1,1'-P(<i>t</i> -Bu) ₂ -ferrocene	20
6	Ni(acac) ₂	H ₃ CC(CH ₂ PPh ₂) ₃	21
7	Ni(acac) ₂	(<i>R</i>)-QUINAP	23
8	Ni(acac) ₂		62
9	NiCl ₂ ·DME		71
10	Ni(acac) ₂	PPh ₃	83
11	NiCl ₂ ·DME	DPE-Phos	92
12	Ni(acac) ₂	DPE-Phos	100

^aGC yield using tridecane as internal standard.

groups are now readily available.⁷ We wish to report herein a general cross-coupling reaction between various thiomethyl-substituted *N*-heterocycles and functionalized aryl-, heteroaryl-, benzylic- and alkylzinc halides using a cheap Ni catalyst. In preliminary studies, we have screened several common nickel salts and phosphine ligands in the model reaction between 2-thiomethylpyridine (1) and 4-methylphenylzinc iodide (2). In the absence of a Pd or Ni catalyst system, no cross-coupling was observed.⁸ Initial attempts with 1 mol % Ni(PPh₃)₂Br₂⁹ without any added ligand gave only 14% yield of the cross-coupling product 3 after 9 h at 25 °C (Table 1, entry 1). NiCl₂·DME¹⁰ furnished the 2-arylated pyridine 3 in 71% yield under these conditions (entry 9). This yield dropped dramatically when 2 mol

SCHEME 1. Ni-Catalyzed Cross-Coupling Reaction of Thiomethyl-Substituted Heterocycles with Functionalized Organozinc Reagents



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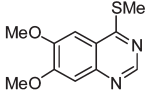
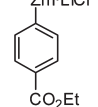
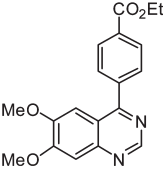

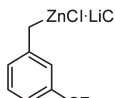
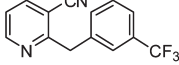

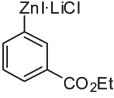
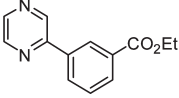

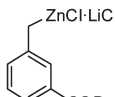
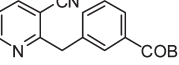
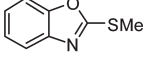

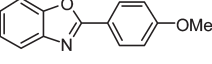
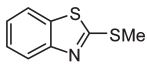
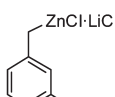
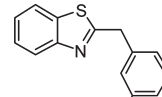
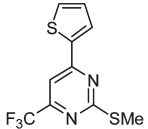
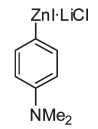
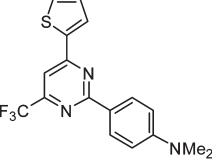

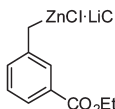
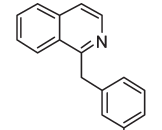
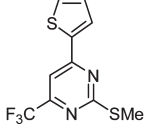
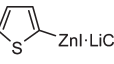
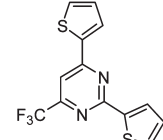
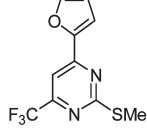
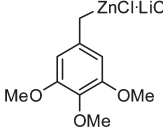
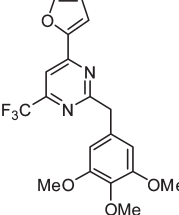
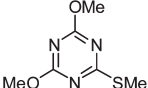
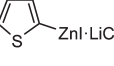
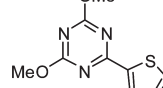
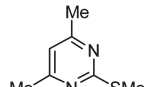
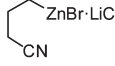
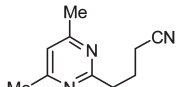
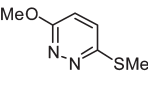
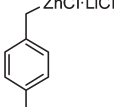
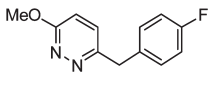
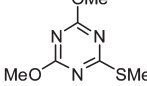
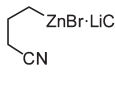
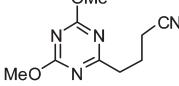

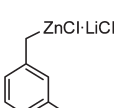
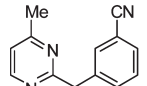
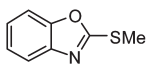
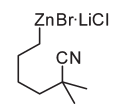
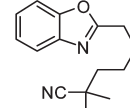
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TABLE 2. Reaction of Thiomethyl-Substituted Heterocycles (4) with Organozinc Reagents (5)

Entry	Electrophile	Zinc reagent	Product, reaction time, yield ^a	Entry	Electrophile	Zinc reagent	Product, reaction time, yield ^a
1			 6a: 24 h, 82%	9			 6i: 8 h, 73%
2			 6b: 14 h, 74%	10			 6j: 5 h, 79%
3			 6c: 3 h, 81%	11			 6k: 48 h, 70%
4			 6d: 6 h, 96%	12			 6l: 48 h, 91%
5			 6e: 16 h, 94%	13			 6m: 24 h, 89%
6			 6f: 16 h, 87%	14			 6n: 48 h, 84%
7			 6g: 5 h, 74%	15			 6o: 48 h, 68%
8			 6h: 7 h, 94%	16			 6p: 12 h, 82%

^aYield of analytically pure product.

% of 1,1,1-tris(diphenylphosphino)ethane was added (entry 2) but increased to 92% in the presence of 2 mol % of bis[2-(diphenylphosphino)phenyl]ether (DPE-Phos) (entry 11).¹¹

The use of inexpensive Ni(acac)₂ led to further improvements, and after testing different ligands, including QUINAP,¹² 1,1'-bis-(di-*tert*-butylphosphino)ferrocene,¹³ and also carbene ligands

such as IMes·HCl,¹⁴ we have found that the most efficient and robust system is Ni(acac)₂ (1 mol %) associated with DPE-Phos (2 mol %), giving quantitative yield of **3** after 9 h at 25 °C (entry 12).¹⁵ Using Ni(acac)₂ (2.5 mol %) and DPE-Phos (5.0 mol %)¹⁶ a broad reaction scope was achieved and most cross-couplings could be completed in 3–48 h at 25 °C (Scheme 1).

Thus, the cross-coupling proceeds well with a range of functionalized aryl- and heteroarylzinc reagents.¹⁷ The reaction of 6,7-dimethoxy-4-(methylthio)quinazoline (**4a**) with 4-ethoxycarbonylphenylzinc iodide (**5a**) provided the functionalized quinazoline **6a** in 82% yield (entry 1 of Table 2). The thiomethyl-substituted pyrazine (**4b**) reacted with 3-ethoxycarbonylphenylzinc iodide (**5b**), providing pyrazine **6b** in 74% yield (entry 2). Electron-rich zinc reagents (**5c,d**) reacted smoothly with benzoxazole **4c** and the disubstituted pyrimidine **4d**, leading to the polyfunctional heterocycles **6c** and **6d** in 81–96% yield (entries 3 and 4). The reaction of trifluoromethylated pyrimidine **4d** with 2-thienylzinc iodide (**5e**) gave the pyrimidine **6e** in 94% yield (entry 5). This heteroaryl zinc reagent also underwent cross-coupling with dimethoxy-substituted triazine (**4e**), yielding the trisubstituted product **6f** in 87% yield (entry 6).

The reaction protocol could be applied to benzylic zinc reagents.¹⁸ The thiomethylated pyridazine **4f** reacted with 4-fluorobenzylzinc chloride (**5f**), furnishing the pyridazine **6g** in 74% yield (entry 7). Similarly, the pyrimidine **4g**, pyridine **4h**, benzothiazole **4i**, and isoquinoline **4j** could be cross-coupled with benzylic zinc reagents bearing sensitive functional groups such as an ester, a nitrile, a ketone, or a trifluoromethyl group, leading to the heterocyclic diarylmethanes **6h–l** in 70–94% yield (entries 8–12). Also, 4-(2-furyl)-2-methylthio-6-trifluoromethylpyrimidine (**4k**) could readily be functionalized using the electron-rich benzylic zinc reagent **5k**, providing the pyrimidine **6m** in 89% yield (entry 13).

Furthermore, this Ni-catalyzed cross-coupling reaction also takes place with alkylzinc reagents.¹⁷ Hence pyrimidine **4l** reacted with 4-cyanopropylzinc bromide (**5l**), furnishing the alkylated product **6n** in 84% yield (entry 14). This

alkylzinc bromide underwent also a smooth cross-coupling with the 2,4,6-trisubstituted triazine **4e**, affording the functionalized triazine **6o** in 68% yield (entry 15). Finally, the reaction of 2-(methylthio)-1,3-benzoxazole (**4c**) with 5-cyano-5-methylhexylzinc bromide (**5m**) provided the alkylated benzoxazole **6p** in 82% yield (entry 16).

In summary, we have developed a novel Ni-catalyzed cross-coupling reaction that uses the inexpensive and commercially available Ni(acac)₂/DPE-Phos system (2.5 and 5 mol %) and takes place at room temperature, furnishing the expected heterocyclic products in 68–96% yield. A wide range of functional groups is tolerated, and various kinds of zinc reagents (alkyl, aryl, heteroaryl, and benzylic) can be utilized.

Experimental Section

Representative Preparation of 2-(3-pentanoylbenzyl)nicotinonitrile (6j). In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar were dissolved 2-(methylthio)nicotinonitrile (**4h**) (150 mg, 1.00 mmol), Ni(acac)₂ (6.4 mg, 2.5 mol %), and DPE-Phos (27 mg, 5.0 mol %) in THF (1 mL). After 10 min of stirring, (3-pentanoylbenzyl)zinc chloride (**5i**) (3.41 mL, 1.50 mmol, 0.44 M in THF) was added dropwise, and the reaction mixture was stirred for 5 h at room temperature until GC analysis of a hydrolyzed aliquot showed full conversion of the electrophile. The reaction mixture was quenched with saturated aqueous K₂CO₃ solution (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na₂SO₄), and the solvent was removed in vacuo. Purification by flash chromatography (silica gel, pentane/Et₂O 4:6) afforded the pyridine **6j** (221 mg, 79%) as a clear oil. ¹H NMR (CDCl₃, 600 MHz) δ (ppm) 0.92 (t, *J* = 7.31 Hz, 3H), 1.32–1.44 (m, 2H), 1.63–1.73 (m, 2H), 2.93 (t, *J* = 7.43 Hz, 2H), 4.43 (s, 2H), 7.28 (dd, *J* = 7.80, 4.83 Hz, 1H), 7.36–7.41 (m, 1H), 7.53–7.57 (m, 1H), 7.79–7.83 (m, 1H), 7.91–7.96 (m, 2H), 8.73 (dd, *J* = 4.83, 1.36 Hz, 1H). ¹³C NMR (CDCl₃, 150 MHz) δ (ppm) 13.9 (CH₃), 22.4 (CH₂), 26.4 (CH₂), 38.3 (CH₂), 42.8 (CH₂), 109.2, 116.7, 121.5 (CH), 126.6 (CH), 128.7 (CH), 128.9 (CH), 133.5 (CH), 137.5, 137.8, 140.7 (CH), 152.6 (CH), 162.9, 200.3. IR (Diamond-ATR, neat) $\tilde{\nu}$ /cm⁻¹ 2956 (m), 2931 (m), 2870 (w), 2227 (w), 1680 (vs), 1580 (m), 1564 (m), 1429 (s), 1265 (m), 1255 (m), 1225 (m), 1174 (m), 1157 (m), 1093 (m), 804 (s), 776 (m), 712 (m), 691 (s). MS (EI, 70 eV) *m/z* (%) 278 (M⁺, 13), 237 (7), 236 (40), 235 (11), 222 (15), 221 (100), 219 (7), 194 (6), 193 (23), 192 (32). HRMS (EI) calcd for C₁₈H₁₈N₂O, 278.1419; found, 278.1417 (M⁺).

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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>.

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