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PALLADIUM-CATALYZED COUPLING OF *N*-HETEROARYL SULFIDES WITH ORGANOZINC REAGENTS†

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Abstract – The palladium-catalyzed cross-coupling of *N*-heteroaryl sulfides with organozinc reagents was developed. Scope and limitation of the reaction regarding generality of zinc reagents and substrate were also investigated.

Transition-metal-catalyzed cross-coupling of organometallic reagents are one of the most versatile and reliable methods to form carbon-carbon σ-bond. While a number of reactions using various substrates including *sp*^{2}-carbon halides or the corresponding pseudo-halides have been developed,[1] only a limited examples of reactions using sulfur containing substrates have been so far reported, for example, Ni-catalyzed cross-coupling of alkenyl or aryl sulfides with Grignard reagents.[2,3] Among sulfur containing compounds, thiol esters have recently attracted considerable attention as substrates for transition-metal-catalyzed cross-coupling.[4,5] After the seminal contribution in this area by Marchese and co-workers who have described Fe(acac)$_3$-catalyzed coupling of thiol esters with Grignard reagents,[6] we have developed a highly chemoselective Pd-catalyzed reduction of thiol esters to aldehyde with Et_3SiH[7] and cross-coupling of thiol esters with organozinc reagents[8] or terminal acetylenes[9] (Scheme 1) to form ketones or alkynyl ketones, respectively.[5,10] In addition, Liebeskind and co-workers reported Cu-mediated Suzuki coupling[11] and Stille coupling of thiol esters.[12] Mechanistically, these palladium-catalyzed cross-couplings of thiol esters would be initiated by oxidative addition of the *sp*^{2} carbon-sulfur bond to Pd(0) to generate acyl palladium species,[13] followed by transmetallation and reductive elimination

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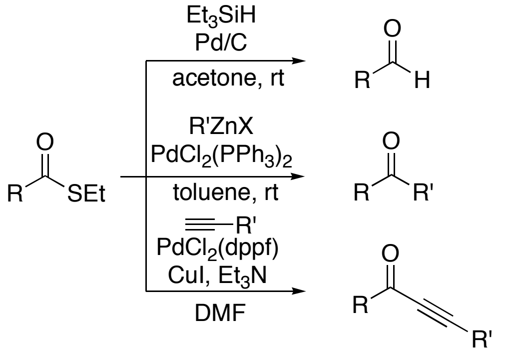
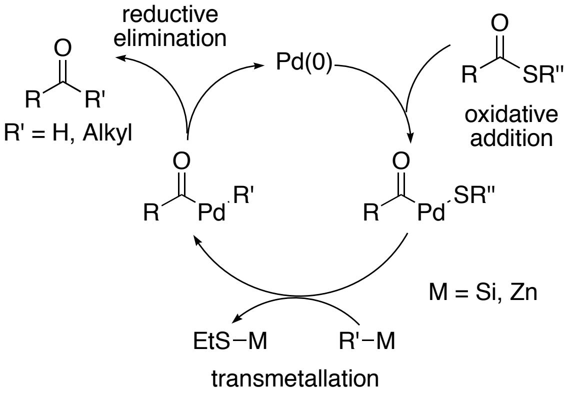
†This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75 years old birthday.



Scheme 1. Palladium-catalyzed transformation of thiolesters

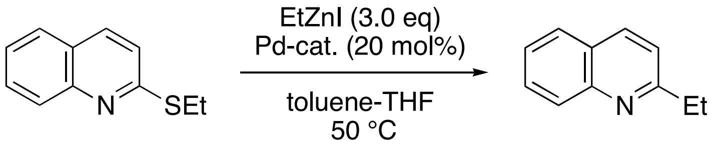


Scheme 2. Plausible mechanisms of palladium-catalyzed transformation of thiol esters

leading to the corresponding aldehydes or ketones (Scheme 2). We considered that, in analogy to the reaction of thiol esters, the *sp*^{2} carbon-sulfur bond of thioimidates should also oxidatively add to Pd(0), and subsequent transmetallation and reductive elimination should furnish imine derivatives. This concept has already been realized using several *N*-heteroaryl sulfides having C-S bond at the α-position to the nitrogen. For example, Liebeskind demonstrated Suzuki coupling[14] and Stille coupling[15] with *N*-heteroaryl sulfide under the copper-mediated reaction conditions. Casalnuovo reported palladium-mediated coupling of *N*-heteroaryl sulfide with benzylzinc reagent.[16] While these methodologies are useful to incorporate *sp*, *sp*^{2}, or benzyl group to *N*-heteroaryl structure, it would be difficult to apply to introduce highly functionalized alkyl chains. Under these backgrounds, we investigated a palladium-catalyzed coupling of *N*-heteroaryl compound having thioimidate structure with organozinc reagents. We report herein development of the highly versatile and mild coupling reaction of *N*-heteroaryl sulfides with organozinc reagents and its general applicability.

By choosing the 2-(ethylthio)quinoline as a test substrate, we initially examined a reaction with EtZnI under the typical conditions utilized for the ketone synthesis with thiol ester (Table 1).[9] As we expected, 2-ethylquinoline was obtained by heating a THF solution of 2-(ethylthio)quinoline and EtZnI in the presence of catalytic $PdCl_2(PPh_3)_2$ at 50 °C although the yield was as low as 43% (entry 1). Screening of various palladium catalysts revealed that the yield was improved to 69% by using $Pd(PPh_3)_4$ (entry 2) and furthermore, to 87% with $PdCl_2$(dppf) (entry 3). Other catalysts such as combinations of $Pd_2(dba)_3$ and DPPF, PCy_3, or $P(2\text{-fulyl})_3$ and Pd-C did not provide better results (entries 4-7). In the absence of palladium catalyst, no product was obtained indicating that the reaction mechanism involves a Pd-catalysis instead of an addition-elimination process (entry 8). In addition, we observed significant solvent effects on the rate of the reaction (Table 2). While comparable yields of the desired coupling product was obtained by reaction in various solvents, more polar solvents required longer time to complete the reaction.

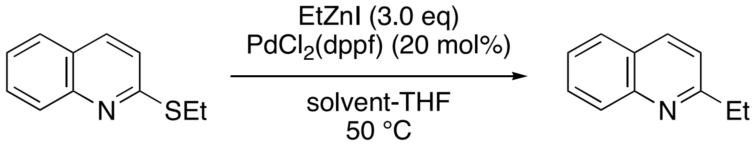
Table 1. Pd-catalyzed coupling reaction of 2-(ethylthio)quinoline with EtZnI[a]



entry	Pd catalyst	time (min)	yield (%)
1	$PdCl_2(PPh_3)_2$	120	43
2	$Pd(PPh_3)_4$	100	69
3	$PdCl_2$(dppf)	15	87
4	$Pd_2(dba)_3$, DPPF[b,c]	120	no reaction
5	$Pd_2(dba)_3$, PCy_3[b,d]	120	26
6	$Pd_2(dba)_3$, P(2-furyl)$_3$[b,d]	120	14
7	Pd-C	270	no reaction
8	none	120	no reaction

[a] Reaction was carried out with THF solutin of EtZnI (1.0 M) in toluene under Ar. [b] $Pd_2(dba)_3$ (10 mol%) was used. [c] DPPF (0.25 equiv) was used. [d] Ligand (0.5 equiv) was used.

Table 2. Pd-catalyzed coupling reaction of 2-(ethylthio)quinoline with EtZnI[a]

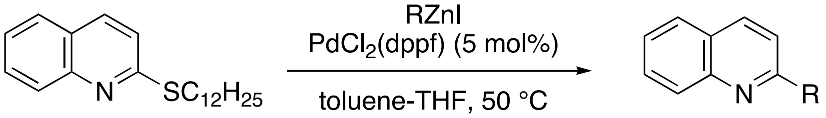


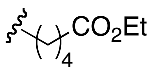
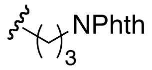
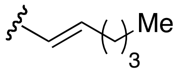
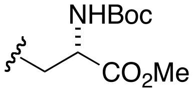
entry	solvent	time (min)	yield (%)
1	toluene	15	87
2	benzene	20	74
3	CH_2Cl_2	20	64
4	CH_3CN	20	62
5	Et_2O	30	64
6	THF	60	75
7	DMF	120	75

[a] Reaction was carried out with THF solution of EtZnI (1.0 M) in toluene under Ar.

While we successfully established the coupling conditions, a disadvantage of this reaction for practical use, namely, unpleasant odor due to ethanethiol during preparation of substrates and work-up, had remained to be improved. Thus, we then investigated a modification of our protocol using odorless dodecanethiol.[17,18] The 2-(dodecylthio)quinoline, which was prepared from 2-chloroquinoline and dodecanethiol, was subjected to the coupling conditions with ethylzinc iodide in toluene-THF (Table 3, entry 1). The desired 2-ethylquinoline was obtained in excellent yield although reaction became relatively slow.

Table 3. Coupling reaction of several organozinc reagents[a]



entry	R	eq	time (min)	yield (%)	entry	R	eq	time (min)	yield (%)
1	Et	2.0	45	91	4		2.0	90	96
2	*i*-Bu	2.0	240	90	5		2.0	180	82
3		3.0	50	47	6		6.0	180	43 (78)[b,c]

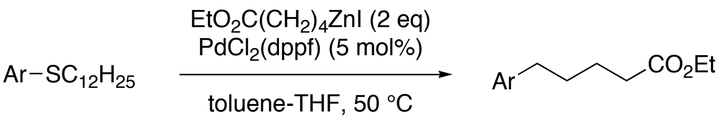
[a] Reaction was carried out with THF solution of zinc reagent in toluene (0.3 M final concentration corresponding to aryl sulfide) under Ar.
[b] Yield in the parenthesis is based on the recovered starting material. [c] >99% ee.

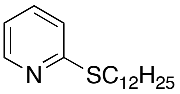
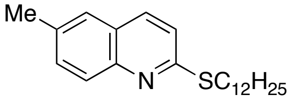
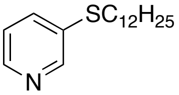
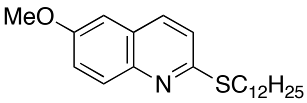
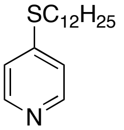
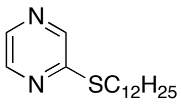
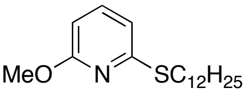
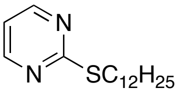
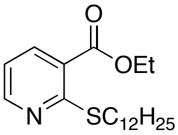
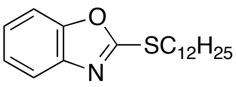
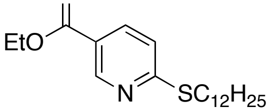
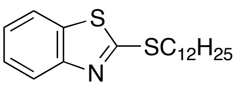
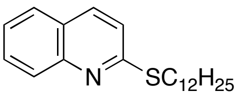
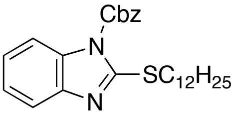
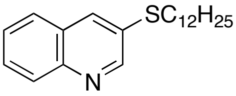
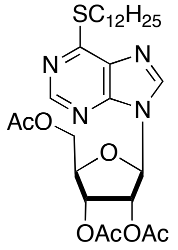
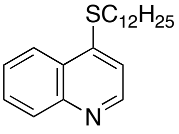
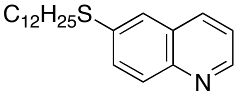
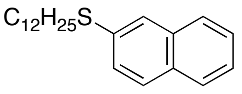
Given the encouraging results, we next examined the reaction with various zinc reagents (Table 3).[19] In addition to alkylzinc reagents (entries 1 and 2), alkenylzinc reagent gave the coupling product in modest yield. It is notable that functionalized alkylzinc reagents including the one bearing terminal ester (entry 4), protected primary amine (entry 5), and α-amino ester functionalities (entry 6) were amenable to the coupling reaction providing the corresponding functionalized quinoline derivatives.

The generality of our method has also been tested by using wide range of *N*-heteroaryl sulfides (Table 4). Interestingly, not only 2-(dodecylthio)pyridine, but also 3- and 4-(dodecylthio)pyridines smoothly coupled with the zinc reagent to provide the corresponding product in good to excellent yields (entries 1-3).[20] While prolonged reaction time was required, pyridine derivative having electron-withdrawing group afforded coupling product in good yields (entries 5 and 6). Surprisingly, reactions of a series of quinoline derivatives revealed that in addition to 2-, 3-, and 4-(dodecylthio)quinoline (entries 6-8), 6-(dodecylthio)quinoline also served as a good substrate for the coupling reaction (entry 10). On the other hand, no coupling product was obtained proceeded with 2-(dodecylthio)naphthalene even after 6 hours (entry 19).[21] Furthermore, the reaction conditions was applicable to other *N*-hetroaryl sulfides such as pyrazine, pyrimidine, benz[*d*]oxazole, benzo[*d*]thiazole, benz[*d*]imidazole derivatives (entries 13-17). Most significantly, this protocol is amenable to introduce a substituent on purine moiety of an adenosine derivative, demonstrating mildness and versatility of the reaction conditions (entry 18).

In conclusion, we have developed the palladium-catalyzed cross-coupling of *N*-heteroaryl sulfides with organozinc reagents. The reaction proved to be applicable to introduce functionalized alkyl chains to a wide range of *N*-heteroaryl sulfides with a various substitution patterns.[22] By using dodecanethiol for the preparation of substrates, we successfully eliminated the unpleasant odor due to thiol by-products.

Table 4. Palladium-catalyzed coupling reaction of *N*-heteroaryl sulfides with $IZn(CH_2)_4CO_2Et$[a]



entry	substrate	time (min)	yield (%)	entry	substrate	time (min)	yield (%)
1		80	92	11		80	96
2		40	80	12		80	95
3		30	74	13		60	97
4[b]		45	99	14		25	83
5[c]		360	72	15		90	98
6		100	85	16		150	88
7		90	96	17		240	48
8		45	100	18		120	70
9		75	67				
10[b]		45	91	19		360	no reaction

[a] Reaction was carried out with THF solution of zinc reagent in toluene (0.3 M final concentration corresponding to heteroaryl sulfide) under Ar. [b] The reaction was carried out at 100 °C. [c] The reaction was carried out at 80 °C.

ACKNOWLEDGEMENTS

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19. **General procedure for the coupling reaction of *N*-heteroaryl sulfide with zinc reagent**: Under an argon atmosphere, a 0.95 M solution (1.29 mL, 1,22 mmol) of (5-ethoxy-5-oxopentyl)zinc(II) iodide in tetrahydrofuran was added to a mixture of 2-(dodecylthio)quinoline (202 mg, 0.61 mmol, prepared from 2-chloroquinoline and 1-dodecanethiol with NaH in DMF at 0 °C to reflux, 92% isolated yield) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25.0 mg, 0.031 mmol) in 0.75 mL of toluene. The mixture was stirred and heated at 50 °C for 90 min. The reaction

mixture was diluted with EtOAc and the reaction was quenched by addition of a saturated aqueous sodium hydrogen carbonate. The aqueous layer separated was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30% EtOAc-hexane) to provide ethyl 5-(quinolin-2-yl)pentanoate (150 mg, 0.58 mmol, 96%) as a pale yellow oil. IR (neat, cm^{-1}): 2943, 1732, 1606, 1502, 1375, 1306, 1184, 827, 760; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.68 (ddd, J = 8.4, 6.8, 1.6 Hz, 1H), 7.49 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.00 (t, J = 7.8 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.92-1.82 (m, 2H), 1.81-1.70 (m, 2H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 162.3, 147.8, 136.2, 129.3, 128.8, 127.4, 126.7, 125.7, 121.3, 60.2, 38.8, 34.1, 29.3, 24.7, 14.2; HRMS (FAB): Calculated for $C_{16}H_{20}NO_2$ $(M+H)^+$, 258.1494; Found 258.1495.

20. Casalnuovo and co-workers also examined coupling reaction of a series of 2-, 3-, and 4-(methythio)pyridines with benzylzinc bromide (Ref. 16). However, they reported that no reaction was observed in the case of 3-(methylthio)pyridine.
21. To the best of our knowledge, this is the first example of palladium-mediated coupling of *N*-heteroaryl sulfide, which has alkylthio group on the carbocyclic ring. While the presence of nitrogen atom in the ring is indispensable for the coupling reaction (Table 4, entry 10 vs. 19), a detailed explanation of this observation is not possible at this point.
22. The reaction we have established in this work was also applicable to simple thioimidates to form the corresponding imines.