Title	Nickel–NHC-Catalyzed Cross-Coupling of 2-Methylsulfanylbenzofurans with Alkyl Grignard Reagents
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Ni-NHC-catalyzed Cross-coupling of 2-Methylsulfanylbenzofurans with Alkyl Grignard Reagents

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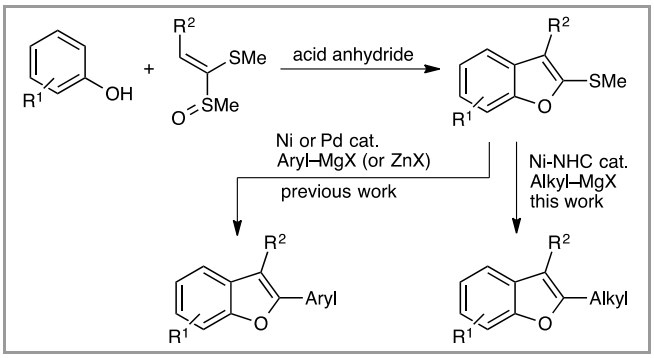
Abstract: $NiCl_2(PPh_3)(IPr)$ catalyzes cross-coupling reactions of 2-methylsulfanylbenzofurans with alkyl Grignard reagents, which other nickel complexes such as $NiCl_2$(dppe) failed to achieve. The alkylation is applicable to the synthesis of a couple of protein tyrosine phosphatase inhibitors, 3-(4-biphenylyl)-2-alkylbenzofurans.

Key words: Nickel, Alkylation, Cross-coupling, Sulfide, Homogeneous catalysis

Cross-coupling reactions of organosulfur compounds date back to 1979, when Takei and Wenkert independently reported $NiCl_2(PPh_3)_2$-catalyzed arylation of aryl or alkenyl sulfides with Grignard reagents.[1] Despite subsequent extensive studies since then,[2–4] cross-coupling of aryl sulfides still remains in its infancy compared with the mature cross-coupling of aryl halides. The immaturity would be mostly attributable to 1) slow oxidative addition of their rather strong C(sp^2)–S bonds, 2) reluctant transmetalation due to high affinity between a transition metal and sulfur in an oxidative adduct, and 3) catalyst poisoning by sulfur compounds. New reaction conditions for more efficient and robust cross-coupling of aryl sulfides with a sustainable metal catalyst have thus been awaited.

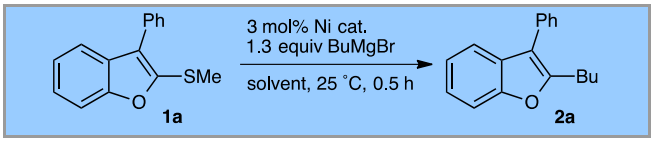
We have been interested in extended Pummerer reactions[5] of ketene dithioacetal monoxides[6,7] and recently developed an efficient and modular access to multisubstituted benzofurans through Pummerer annulation[6e–g] (Scheme 1). Since our annulation always leads to formation of 2-methylsulfanyl-substituted benzofurans, transformations of the sulfur moieties should dictate the usefulness of our methodology. Indeed, with state-of-the-art transition metal catalysis, cross-coupling arylation of the products yielded highly fluorescent compounds[6e–g] as well as anticancer agents.[6g] Along this line, we report herein that a Ni-NHC (N-heterocyclic carbene) complex is an effective catalyst for cross-coupling alkylation[8] of 2-methylsulfanyl-substituted benzofurans, which was applied to efficient synthesis of protein tyrosine phosphatase (PTP) 1B inhibitors.

Cross-coupling butylation of benzofuran **1a** was chosen as a model reaction to probe a potent catalytic system. The results of catalyst optimization are summarized in Table 1. Although nickel phosphine complexes are known to promote cross-coupling of aryl sulfides,[1,2a–e] the transformation of **1a** is not trivial. Attempted butylation with nickel diphosphine complexes resulted in no conversions (entry 1–3). As **1a** is regarded as a bulky aryl sulfide due to the neighboring phenyl group, we envisioned a Ni-NHC complex bearing a bulky NHC to be suitable.[9,10] Indeed, a commercially available nickel complex $NiCl_2(PPh_3)(IPr)$[11] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] catalyzed the desired alkylation very smoothly to afford **2a** in 95% yield (entry 4). Finally, replacing toluene with THF as a solvent led to quantitative formation of **2a** in 30 min (entry 5). In the absence of any catalysts, no reaction took place (entry 6).



Scheme 1 Pummerer annulation/cross-coupling strategy for tailor-made synthesis of benzofurans

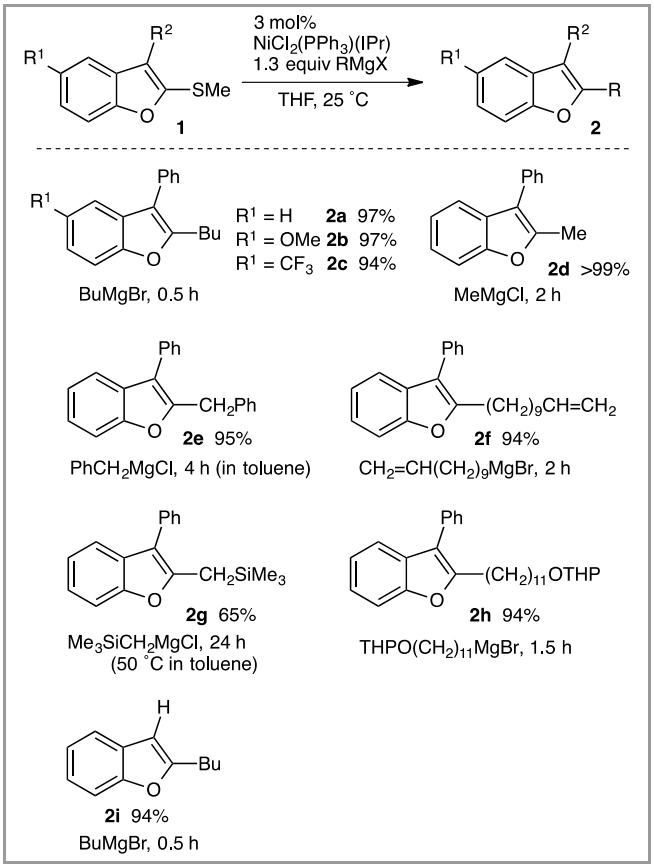
Table 1 Optimization of catalyst for alkylation



entry	cat.	solvent	results (by NMR)
1	$NiCl_2(PPh_3)_2$	toluene	no conversion
2	$NiCl_2$(dppe)	toluene	no conversion
3	$NiCl_2$(dppp)	toluene	no conversion
4	$NiCl_2(PPh_3)$(IPr)	toluene	95% yield of **2a**
5	$NiCl_2(PPh_3)$(IPr)	THF	>99% yield of **2a**
6	none	THF	no conversion

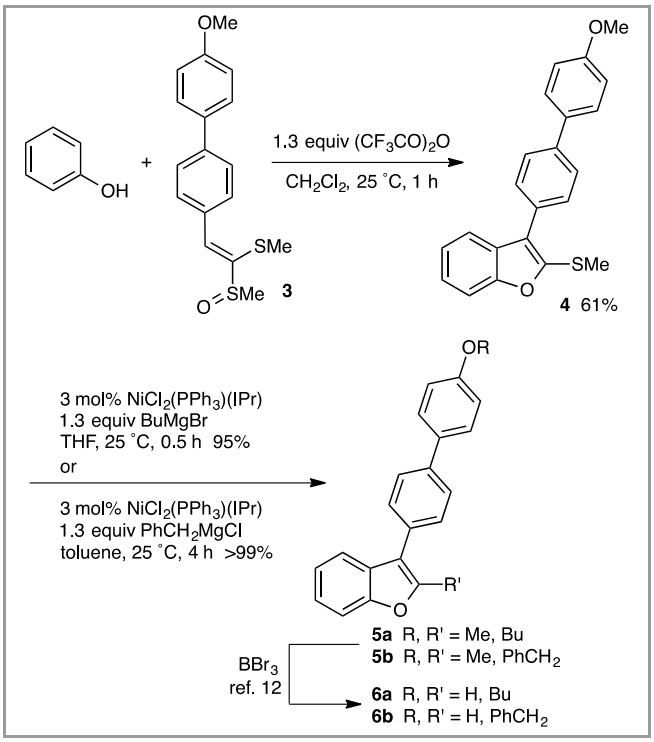
The scope of the alkylation is summarized in Scheme 2. Electronically biased substituents at the 6 position have virtually no influence on the efficiency of the reaction (**2b** and **2c**). The smallest methyl (**2d**),

unsaturated 10-undecenyl (**2f**), and THP-protected 11-hydroxyundecyl (**2h**) groups were installed easily. Benzylmagnesium chloride was less reactive and required 4 h to reach completion (**2e**). Trimethylsilylmethylmagnesium chloride was much more reluctant to afford **2g** in 24 h even at 50 ˚C. It is worth noting that 2-methylsulfanylbenzofuran, which has no substituent at the 3 position, totally resisted alkylation with $NiCl_2$(dppe) but underwent very smooth alkylation with $NiCl_2(PPh_3)$(IPr) to yield **2i**.



Scheme 2 Scope of alkylation.

A series of 3-(4-biphenylyl)-2-alkylbenzofurans are attracting significant attention since they serve as potent inhibitors of PTP 1B.[12] In the previous report, each alkylbenzofuran in the library was prepared via a lengthy linear route. Advantageously, our approach to 2-alkylbenzofurans has proved to be more efficient for the synthesis of 3-(4-biphenylyl)-2-alkylbenzofurans bearing variety in the alkyl chain. Ketene dithioacetal monoxide **3** was prepared through the Knoevenagel condensation in one step according to the literature procedure.[7a] Phenol underwent the Pummerer annulation[6g] with **3** by means of trifluoroacetic anhydride to afford 2-methylsulfanylbenzofuran **4** in 61% yield. The following cross-coupling butylation and benzylation were successful, yielding intermediates **5a** and **5b**, respectively, in a diversity-oriented fashion. Benzofurans **5a** and **5b** are key intermediates that should undergo demethylation as the last step to yield potent PTP 1B inhibitors **6**.[12]



Scheme 3 Formal synthesis of PTP inhibitors.

In summary, we have developed highly efficient cross-coupling alkylation of benzofuryl sulfides with a nickel-NHC catalyst and applied it to formal synthesis of PTP 1B inhibitors. Investigations to find efficient transformations of organosulfur compounds with a sustainable transition metal catalyst are underway in our laboratory.

The butylation of **1a** is representative. $NiCl_2(PPh_3)$(IPr) (11.7 mg, 0.015 mmol) was placed in a dry Schlenk tube equipped with a magnetic stir bar and a rubber septum under argon. A solution of methylsulfanylbenzofuran **1a** (120 mg, 0.50 mmol) in THF (5.0 mL) was then added. Butylmagnesium bromide (0.60 M in THF, 1.0 mL, 0.60 mmol) was then added to the mixture and the resulting mixture was stirred for 30 min at 25 ˚C. The mixture was filtered through a pad of silica gel with copious washings with CH_2Cl_2. The filtrate was evaporated to leave a crude oil. ^{1}H NMR analysis of the oil revealed the yield of **2a** was quantitative. Silica gel column purification (n-hexane) afforded butylated benzofuran **2a** (121 mg, 0.48 mmol) in 97% yield as a colorless oil. 2-Butyl-3-phenylbenzo[*b*]furan (**2a**): ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.60 (d, 1H, *J* = 7.8 Hz), 7.54–7.50 (m, 5H), 7.40 (t, 1H, *J* = 6.6 Hz), 7.30 (t, 1H, *J* = 6.6 Hz), 7.25 (t, 1H, *J* = 7.8 Hz), 2.90 (t, 2H, *J* = 7.8 Hz), 1.81 (quint, 2H, *J* = 7.2 Hz), 1.44 (sex, 2H, *J* = 7.2 Hz), 0.95 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 155.46, 154.18, 133.07, 129.25, 129.06, 128.86, 127.12, 123.66, 122.68,

119.57, 116.93, 110.97, 30.68, 26.66, 22.61, 13.95. IR (cm^{-1}) 2956, 2928, 2871, 1610, 1496, 1454, 1255, 1219, 1174, 1012, 969, 769, 700. HRMS (ESI) calcd for $C_{18}H_{18}OH$ ($[M+H]^+$): 281.1536; found 281.1538.

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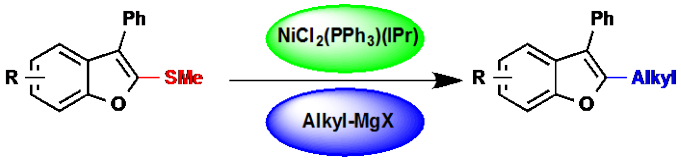
Short title: Ni-catalyzed desulfanylative alkylation



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