

Ni-NHC-catalyzed Cross-coupling of 2-Methylsulfanylbenzofurans with Alkyl Grignard Reagents

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Abstract: NiCl₂(PPh₃)(IPr) catalyzes cross-coupling reactions of 2-methylsulfanylbenzofurans with alkyl Grignard reagents, which other nickel complexes such as NiCl₂(dppe) failed to achieve. The alkylation is applicable to the synthesis of a couple of protein tyrosine phosphatase inhibitors, 3-(4-biphenyl)-2-alkylbenzofurans.

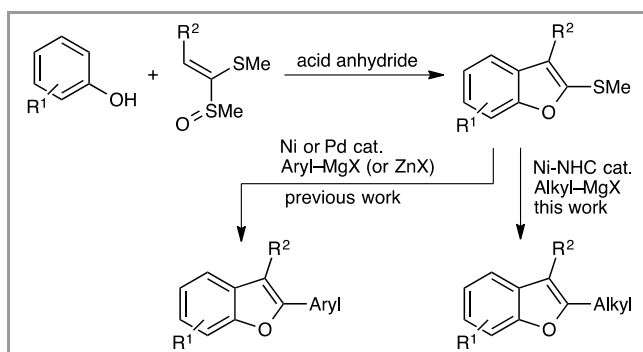
Key words: Nickel, Alkylation, Cross-coupling, Sulfide, Homogeneous catalysis

Cross-coupling reactions of organosulfur compounds date back to 1979, when Takei and Wenkert independently reported NiCl₂(PPh₃)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(sp²)-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 reactions⁵ 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 alkylation⁸ of 2-methylsulfanyl-substituted benzofurans, which was applied to efficient synthesis of protein tyrosine phosphatase (PTP) 1B inhibitors.

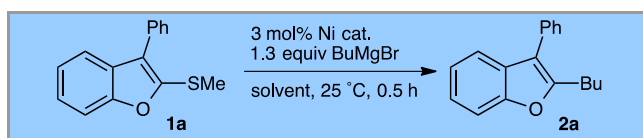
Cross-coupling butylation of benzofuran **1a** was chosen as a model reaction to probe a potent catalytic system. The results of catalyst optimization are summarized in Table 1. Although nickel phosphine complexes are known to promote cross-coupling of

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 NiCl₂(PPh₃)(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

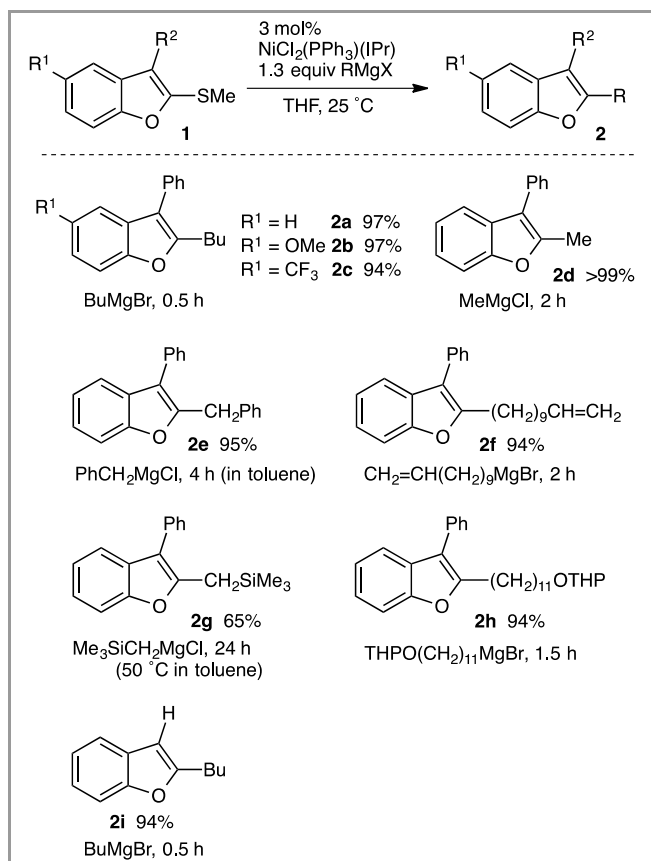
Table 1 Optimization of catalyst for alkylation



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

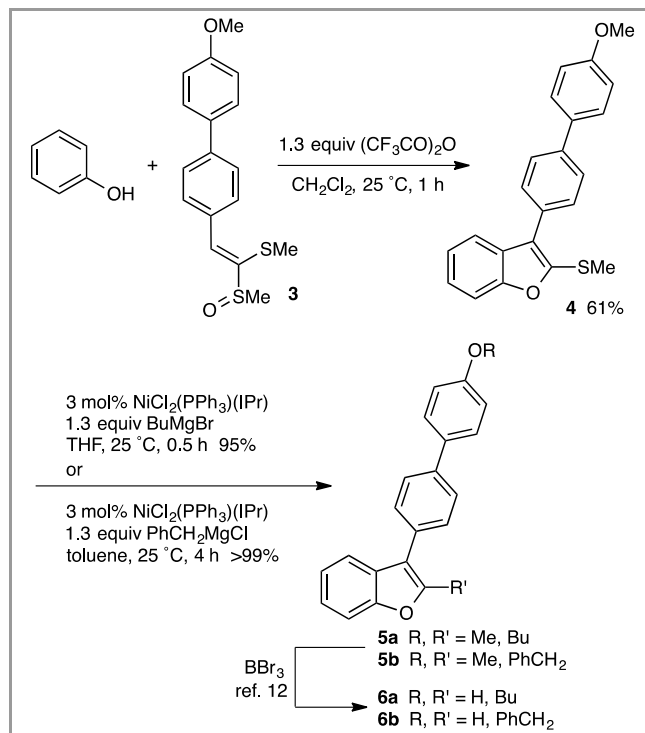
The scope of the alkylation is summarized in Scheme 2. Electronically biased substituents at the 6 position have virtually no influence on the efficiency of the reaction (**2b** and **2c**). The smallest methyl (**2d**),

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-methylsulfanylbzofuran, which has no substituent at the 3 position, totally resisted alkylation with NiCl₂(dppe) but underwent very smooth alkylation with NiCl₂(PPh₃)(IPr) to yield **2i**.



Scheme 2 Scope of alkylation.

A series of 3-(4-biphenyl)-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-biphenyl)-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-methylsulfanylbzofuran **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. NiCl₂(PPh₃)(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 methylsulfanylbzofuran **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 CH₂Cl₂. The filtrate was evaporated to leave a crude oil. ¹H 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**): ¹H NMR (600 MHz, CDCl₃) 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). ¹³C NMR (150 MHz, CDCl₃) δ (ppm) 155.46, 154.18, 133.07, 129.25, 129.06, 128.86, 127.12, 123.66, 122.68,

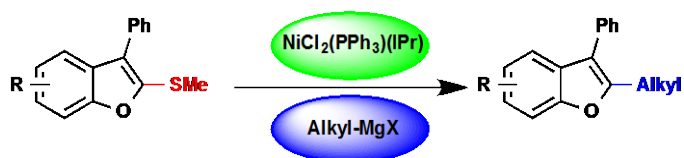
119.57, 116.93, 110.97, 30.68, 26.66, 22.61, 13.95. IR (cm^{-1}) 2956, 2928, 2871, 1610, 1496, 1454, 1255, 1219, 1174, 1012, 969, 769, 700. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{OH}$ ($[\text{M}+\text{H}]^+$): 281.1536; found 281.1538.

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References

- (1) (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 20, 43. (b) Takei, H.; Miura, M.; Sugimura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447. (c) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637.
- (2) Reviews: (a) Sugimura, H.; Okamura, H.; Miura, M.; Yoshida, M.; Takei, H. *Nippon Kagaku Kaishi* **1985**, 416. (b) Naso, F. *Pure Appl. Chem.* **1988**, 60, 79. (c) Luh, T.-Y.; Ni, Z.-J. *Synthesis* **1990**, 89. (d) Luh, T.-Y. *Acc. Chem. Res.* **1991**, 24, 257. (e) Fiandanese, V. *Pure Appl. Chem.* **1990**, 62, 1987. (f) Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, 74, 115. (g) Dubbaka, S. R.; Vogel, P. *Angew. Chem. Int. Ed.* **2005**, 44, 7674. (h) Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2008**, 47, 3674. (i) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, 42, 599. (j) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, 42, 5042. (k) Pan, F.; Shi, Z.-J. *ACS Catal.* **2014**, 4, 280.
- (3) Very recent selected examples: (a) Hooper, J. F.; Young, R. D.; Pernik, I.; Weller, A. S.; Willis, M. C. *Chem. Sci.* **2013**, 4, 1568. (b) Pan, F.; Wang, H.; Shen, P.-X.; Zhao, J.; Shi, Z.-J. *Chem. Sci.* **2013**, 4, 1573. (c) Creech, G. S.; Kwon, O. *Chem. Sci.* **2013**, 4, 2670. (d) Higashino, T.; Rodríguez-Morgade, M. S.; Osuka, A.; Torres, T. *Chem. Eur. J.* **2013**, 19, 10353. (e) Liu, J.-X.; Liu, Y.-J.; Du, W.-T.; Dong, Y.; Liu, J.; Wang, M. *J. Org. Chem.* **2013**, 78, 7293. (f) Quan, Z.-J.; Lv, Y.; Jing, F.-Q.; Jia, X.-D.; Huo, C.-D.; Wang, X.-C. *Adv. Synth. Catal.* **2014**, 356, 325. (g) Sugahara, T.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2014**, 53, 9329. (h) Otsuka, S.; Fujino, D.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Chem. Eur. J.* Early View, DOI: 10.1002/chem.201404380.
- (4) Recent examples of nickel-catalyzed cross-coupling of sulfides: (a) Melzig, L.; Metzger, A.; Knochel, P. *Chem. Eur. J.* **2011**, 17, 2948. (b) Hintermann, L.; Schmitz, M.; Chen, Y. *Adv. Synth. Catal.* **2010**, 352, 2411. (c) Eberhart, A. J.; Imbriglio, J. E.; Procter, D. J. *Org. Lett.* **2011**, 13, 5882. (d) Ma, J.; Peng, L.; Zhang, X.; Zhang, Z.; Campbell, M.; Wang, J. *Chem. Asian J.* **2010**, 5, 2214. (e) Lee, K.; Counciller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, 11, 1457. (f) Ishizuka, K.; Seike, H.; Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, 132, 13117. (g) Murakami, K.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2014**, 53, 7510. (h) Murakami, K.; Yorimitsu, H.; Osuka, A. *Bull. Chem. Soc. Jpn.* in press, DOI:10.1246/bcsj.20140241.
- (5) Reviews: (a) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, 104, 2401. (b) Feldman, K. S. *Tetrahedron* **2006**, 62, 5003. (c) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, 49, 5832. (d) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, 274, 35. (e) *Sulfur-Mediated Rearrangements I*, Schaumann, E. Ed., Springer, **2007**. (f) Yorimitsu, H. *J. Synth. Org. Chem. Jpn.* **2013**, 71, 341.
- (6) (a) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007**, 9, 5573. (b) Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2008**, 37, 786. (c) Kobatake, T.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2010**, 49, 2340. (d) Murakami, K.; Imoto, J.; Matsubara, H.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2013**, 19, 5625. (e) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, 132, 11838. (f) Ookubo, Y.; Wakamiya, A.; Yorimitsu, H.; Osuka, A. *Chem. Eur. J.* **2012**, 18, 12690. (g) Reference 4g and 4h.
- (7) Facile preparation of ketene dithioacetal monoxides: (a) Murakami, K.; Yorimitsu, H.; Osuka, A. *Bull. Chem. Soc. Jpn.* **2013**, 86, 1193. (b) Murakami, K.; Yorimitsu, H.; Osuka, A. *Bull. Chem. Soc. Jpn.* **2014**, 87, 441. (c) Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1972**, 13, 1383. (d) Ogura, K.; Ito, Y.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1979**, 52, 2013.
- (8) Ni-NHC catalysts are known to be more effective than Ni-phosphine catalysts for cross-coupling arylation of organosulfur compounds with aryl Grignard reagents. See references 4b, 4g, and 4h.
- (9) Representative reviews on transition metal-carbene complexes: (a) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, 41, 1440. (b) Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, 251, 874. (c) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, 40, 5151. (d) Wuertz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, 41, 1523. (e) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, 600, 12. (f) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem. Int. Ed.* **2012**, 51, 3314.
- (10) For Ni-NHC complexes: (a) Gu, S.; Ni, P.; Chen, W. *Chin. J. Cat.* **2010**, 31, 875. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, 111, 1346. (c) Han, F.-S. *Chem. Soc. Rev.* **2013**, 42, 5270.
- (11) (a) Matsubara, K.; Ueno, K.; Shibata, Y. *Organometallics* **2006**, 25, 3422. (b) Tanaka, S.; Tanaka, D.; Tatsuta, G.; Murakami, K.; Tamba, S.; Sugie, A.; Mori, A. *Chem. Eur. J.* **2013**, 19, 1658. (c) Iglesias, M. J.; Prieto, A.; Nicasio, M. C. *Org. Lett.* **2012**, 14, 4318.
- (12) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, 43, 1293.

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