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Palladium-Catalyzed Cross-Coupling of Benzyl Thioacetates and Aryl Halides

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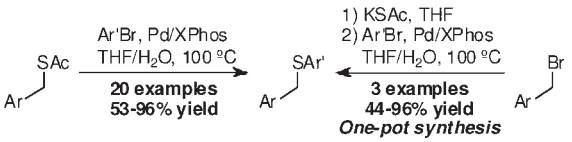
ABSTRACT



A method for preparing benzyl aryl thioethers utilizing an in situ deprotection of benzyl thioacetates as an alternative to free thiols as starting materials has been developed and optimized. Good to excellent yields of diverse benzyl aryl thioethers are obtained with air-stable, odor-free, and easy to prepare thioesters. A one-pot protocol for forming benzyl aryl thioethers from a benzyl halide, potassium thioacetate, and an aryl bromide has also been demonstrated.

The prevalence of alkyl aryl thioethers (and their derivatives) in natural products and pharmaceuticals has led to the development of many methods for C−S bond construction. Metal-catalyzed cross-coupling reactions have proven to be a robust technique,[1] with Pd[2] and Cu[3] emerging as excellent catalysts in various applications.

These methods, however, rely on the use of alkyl thiols, which can be odorous and sensitive to oxidation. To circumvent this issue, diaryl disulfides have been coupled with alkyl halides.[4] There have also been reports of in situ cleavage of thioesters for use in S_NAr reactions.[5] Hartwig and co-workers have used Pd coupling to prepare unsymmetrical biaryl thioethers from aryl halides and TIPS-thiol,[6] while others have utilized copper and a xanthate salt.[7] Potassium thioacetate has also been employed in a Cu-catalyzed coupling with an aryl halide followed by hydrolysis and reaction with an alkyl halide.[8]

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(1) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(2) (a) Fu, C.-F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Tetrahedron* **2010**, *66*, 2119. (b) Lee-Dutra, A.; Wiener, D. K.; Arienti, K. L.; Liu, J.; Mani, N.; Ameriks, M. K.; Axe, F. U.; Gebauer, D.; Desai, P. J.; Nguyen, S.; Randal, M.; Thurmond, R. L.; Sun, S.; Karlsson, L.; Edwards, J. P.; Jones, T. K.; Grice, C. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2370. (c) Harris, R. N., Iii; Stabler, R. S.; Repke, D. B.; Kress, J. M.; Walker, K. A.; Martin, R. S.; Brothers, J. M.; Ilnicka, M.; Lee, S. W.; Mirzadegan, T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3436. (d) Hamada, M.; Nakamura, M.; Kiuchi, M.; Marukawa, K.; Tomatsu, A.; Shimano, K.; Sato, N.; Sugahara, K.; Asayama, M.; Takagi, K. E. A. *J. Med. Chem.* **2010**, *53*, 3154. (e) Fernández-Rodriguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (f) Eichman, C. C.; Stambuli, J. P. *J. Org. Chem.* **2009**, *74*, 4005. (g) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (h) Lee, J.-Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (i) Rabaça, S.; Duarte, M. C.; Santos, I. C.; Pereira, L. C. J.; Fourmigué, M.; Henriques, R. T.; Almeida, M. *Polyhedron* **2008**, *27*, 1999. (j) Fernández-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (k) Fernández-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem.—Eur. J.* **2006**, *12*, 7782. (l) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Breslin, P. *Tetrahedron* **2005**, *61*, 5253. (m) Moreau, X.; Campagne, J. M.; Meyer, G.; Jutand, A. *Eur. J. Org. Chem.* **2005**, 3749. (n) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397. (o) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (p) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (q) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205.

(3) (a) Martinek, M.; Korf, M.; Srogl, J. *Chem. Commun. (Cambridge, U.K.)* **2010**, *46*, 4387. (b) Feng, Y.-S.; Li, Y.-Y.; Tang, L.; Wu, W.; Xu, H.-J. *Tetrahedron Lett.* **2010**, *51*, 2489. (c) Prasad, D. J. C.; Sekar, G. *Synthesis* **2010**, *1*, 79. (d) Kabir, M. S.; Lorenz, M.; Van Linn, M. L.; Namjoshi, O. A.; Ara, S.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3626. (e) Xu, H.-J.; Zhao, X.-Y.; Deng, J.; Fu, Y.; Feng, Y.-S. *Tetrahedron Lett.* **2009**, *50*, 434. (f) Feng, Y.; Wang, H.; Fangfang, S.; Li, Y.; Fu, X.; Jin, K. *Tetrahedron* **2009**, *65*, 9737. (g) Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 1441. (h) Xin, K.; Huang, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2009**, *11*, 338. (i) She, J.; Jiang, Z.; Wang, Y. *Tetrahedron Lett.* **2009**, *50*, 593. (j) Clayden, J.; Senior, J. *Synlett* **2009**, *17*, 2769. (k) Zhao, X.-Y.; Fu, Y.; Feng, Y.-S. *Synlett* **2008**, 3063. (l) Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, 640. (m) Lu, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (n) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (o) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517.

(4) (a) Munbunjong, W.; Lee, E. H.; Ngernmaneerat, P.; Kim, S. J.; Singh, G.; Chavasiri, W.; Jang, D. O. *Tetrahedron* **2009**, *65*, 2467. (b) Peppe, C.; Borges de Castro, L. *Can. J. Chem.* **2009**, *87*, 678. (c) Tang, R.; Zhong, P.; Lin, Q. *Synthesis* **2007**, 85. (d) Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793. (e) Fukuzawa, S.; Tanihara, D.; Kikuchi, S. *Synlett* **2006**, 2145.

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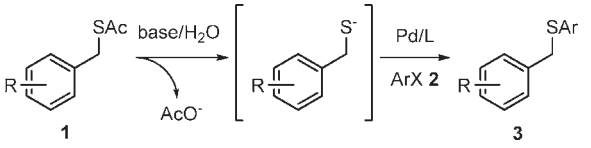
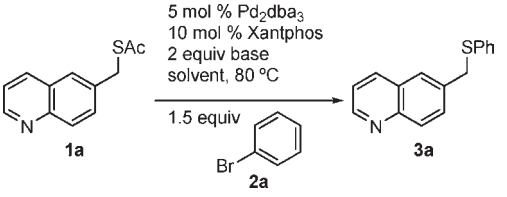
Scheme 1. Proposed Thioacetate Coupling



Recognizing the utility of a protected thiol, we sought to optimize the coupling of *S*-benzyl thioesters with aryl halides, believing that an in situ deprotection would be compatible with known cross-coupling conditions (Scheme 1). The thioacetate protecting group, a common intermediate in the synthesis of thiols in a variety of applications,[9] was chosen because of its ease of installation, simplicity of deprotection, and low molecular weight. Most examples of this transformation describe the proposed coupling as an undesired side reaction[10] or are limited to a single example.[11,12] After considering several known conditions,[3k,l,13] we began our investigations with Pd_2dba_3, Xantphos, and DIPEA in 1,4-dioxane.[2o] Unfortunately, this was not effective in coupling thioacetate **1a** with bromide **2a** (Table 1, entry 1).

To enable this transformation, we examined various bases and solvents. Organic bases such as DIPEA and Me_2NH in various solvents were ineffective (entries 1–4). In light of this, both strong and weak inorganic bases were investigated using wet or dry 1,4-dioxane as a solvent. Aqueous conditions were favored, with the mild base potassium carbonate emerging as the preferred additive (entry 8). The addition of water likely improved the rate of hydrolysis of the thioacetates. A solvent screen revealed aqueous THF as the superior solvent (entry 13), and it was determined that only 1 equiv of base was required to obtain good yields (entry 18). Attempts to convert **1a** to **3a** in the absence of either base or palladium failed to give product. Further experiments (all with 2 equiv of K_2CO_3 in wet THF) revealed that a reaction temperature of 100 °C gave a slightly higher yield (85%), performing the reaction at 60 °C gave a reduced yield (20%), and using $Pd(OAc)_2$ or $PdCl_2$ also provided product (73% and 63%, respectively).

Table 1. Optimization of Thioacetate Coupling with PhBr[a]



entry	base	solvent	water[b]	yield[c] (%)
1	DIPEA	1,4-dioxane	0	0
2	DIPEA	MeOH	0	14
3	DIPEA	1,4-dioxane	4:1	28
4	DMA	1,4-dioxane	0	31
5	NaO^{t}Bu	1,4-dioxane	0	23
6	NaO^{t}Bu	1,4-dioxane	4:1	28
7	K_2CO_3	1,4-dioxane	0	36
8	K_2CO_3	1,4-dioxane	4:1	74
9	KOH	1,4-dioxane	0	66
10	KOH	1,4-dioxane	4:1	61
11	NaOMe	1,4-dioxane	0	19
12	NaOAc	1,4-dioxane	0	0
13	K_2CO_3	THF	4:1	78
14	K_2CO_3	toluene	4:1	42
15	K_2CO_3	MeOH	4:1	0
16	K_2CO_3	DMF	4:1	0
18	**K_2CO_3**[d]	**THF**	**4:1**	**79**
19	K_2CO_3	THF	9:1	60
20	K_2CO_3	THF	1:1	68
21	K_2CO_3	THF	1:9	27

[a] Reactions run on 0.5 mmol of **1a** at 0.4 M for 14–18 h. Reactions were not optimized for time. [b] Ratio of solvent to water. [c] Isolated yield of pure **3a**. [d] Reaction run with 1 equiv of base.

With this optimization in hand, we elected to determine the scope of the reaction using the Pd_2dba_3/Xantphos system and 1 equiv of K_2CO_3 in 4:1 THF/water at 100 °C. To our surprise, initial experiments with **2b** (see Table 2 for structures) provided a 7:1 mixture of the desired product **3b** and compound **3a**. Indeed, **3a** was observed with a variety of aryl bromide substrates even when using rigorously purified materials. At this point, we suspected that the phenyl group found in the **3a** byproduct came from either degradation or transfer of a phenyl group from Xantphos.

By closely monitoring the reaction of **1a** and **2b**, it was determined that **3a** formed concomitantly with **3b**. Meanwhile, subjecting compound **3b** by itself to the standard reaction conditions gave no **3a**, ruling out the degradation of **3b**. Switching from Pd_2dba_3 to $Pd(OAc)_2$ did not change

(5) (a) Miyama, D.; Araoka, F.; Takezoe, H.; Kim, J.; Kato, K.; Takata, M.; Aida, T. *J. Am. Chem. Soc.* **2010**, *132*, 8530. (b) Samaroo, D.; Vinodu, M.; Chen, X.; Drain, C. M. *J. Comb. Chem.* **2007**, *9*, 998. (c) Henke, B. R.; Consler, T. G.; Go, N.; Hale, R. L.; Hohman, D. R.; Jones, S. A.; Lu, A. T.; Moore, L. B.; Moore, J. T.; Orband-Miller, L. A.; Robinett, R. G.; Shearin, J.; Spearing, P. K.; Stewart, E. L.; Turnbull, P. S.; Weaver, S. L.; Williams, S. P.; Wisely, G. B.; Lambert, M. H. *J. Med. Chem.* **2002**, *45*, 5492.

(6) Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355.

(7) Prasad, D. J. C.; Sekar, G. *Org. Lett.* **2011**, *13*, 1008.

(8) van den Hoogenband, A.; Lange, J. H. M.; Bronger, R. P. J.; Stoit, A. R.; Terpstra, J. W. *Tetrahedron Lett.* **2010**, *51*, 6877.

(9) (a) Kimmel, K. L.; Robak, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 8754. (b) DeMartino, J. K.; Hwang, I.; Connelly, S.; Wilson, I. A.; Boger, D. L. *J. Med. Chem.* **2008**, *51*, 5441. (c) Lélias-Vanderperre, A.; Chambron, J.-C.; Espinosa, E.; Terrier, P.; Leize-Wagner, E. *Org. Lett.* **2007**, *9*, 2961. (d) Bodwell, G. J.; Bridson, J. N.; Chen, S.-L.; Poirier, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 4704.

(10) Flatt, A. K.; Dirk, S. M.; Henderson, J. C.; Shen, D. E.; Su, J.; Reed, M. A.; Tour, J. M. *Tetrahedron* **2003**, *59*, 8555.

(11) Linghu, X.; Linn, K.; Maloney, K. M.; McLaughlin, M.; Qian, G. US Patent Application 2010/0234604 A1, 2010.

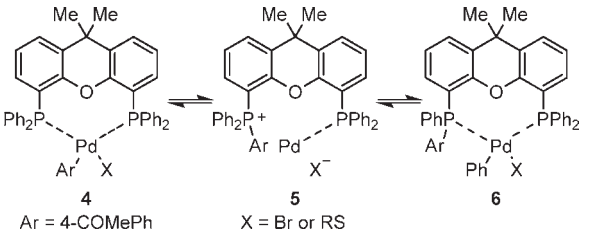
(12) Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371. The cited work was published during the preparation of our manuscript. While our investigation focuses on the use of benzyl thioacetates, Lee and co-workers optimized for aryl thioacetates (broad substrate scope was demonstrated, but only one benzyl aryl thioether was prepared). The conditions used are comparable, although Lee uses DPPF and an anhydrous system. Additionally, both studies demonstrate a one-pot potassium thioacetate based coupling of appropriate substrates. We believe the works to be complementary in scope

(13) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484.

the product distribution, but using commercially available *tert*-butyl Xantphos gave solely compound **3b**. This result suggested a process of aryl−aryl transfer between a phenyl group on Xantphos and Pd-bound **2b**. Such a transfer has been observed previously, mostly with monodentate ligands such as triphenylphosphine.[14] Notably, Hartwig observed an aryl−aryl exchange process while studying palladium-catalyzed C−S coupling reactions,[2q,15] A likely mechanism based on that proposed by Chenard et al. is shown in Scheme 2.[14a]

Initial oxidative addition of **2b** with Xantphos-bound Pd(0) would form **4**, where the ligand X is either bromide or thiolate depending on whether the aryl/aryl exchange process occurs prior to or after the expected σ bond metathesis.[16] Reductive elimination provides species **5**, which then undergoes oxidative addition either at a C−Ph bond (to regenerate **4**) or at the C−Ar bond (providing **6**), with **6** providing **3a**.

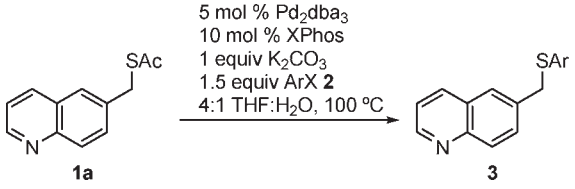
Scheme 2. Proposed Mechanism for Aryl−Aryl Exchange

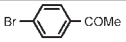
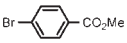
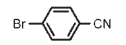
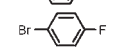
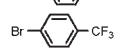
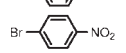
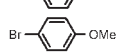
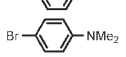
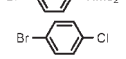
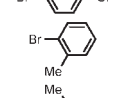
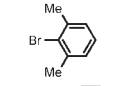
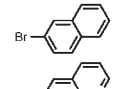
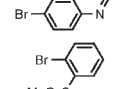
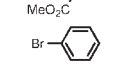
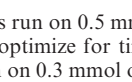


To support this hypothesis, we reacted **1a** with **2a**-d_5 under the previously optimized conditions (Table 1, entry 18); this provided a mixture of 3.5:1 **3a**-d_5:**3a**. The inclusion of **3a** again implicates Xantphos as the source of the phenyl group via an aryl−aryl exchange process. Additionally, ^{31}P NMR analysis of Xantphos heated in the presence of Pd_2dba_3 and excess **2b** confirmed the formation of phosphorus-containing species distinct from **4**.[17] After heating for several hours at 100 °C, we observed several doublets in the ^{31}P NMR spectrum downfield of the both the free and Pd-bound Xantphos singlets. Though not conclusive, this is consistent with aryl−aryl exchange disrupting the symmetry of the phosphorus atoms in Xantphos.

A brief ligand screen showed that XPhos[18] provided good yields of **3b** (66%) under the previous reaction conditions with no formation of **3a**. We proceeded to explore the substrate scope of our optimized one-pot deprotection/cross-coupling reaction (Table 2). These conditions were effective for a diverse array of substrates, including electron-poor (entries 1−6) and electron-rich (entries 7 and 8) aryl bromides. Sterically demanding aryl bromides (entries 10, 11, and 14) coupled efficiently, as did base-sensitive functional groups including methyl esters and nitriles (entries 2, 3, and 14). No hydrolysis of methyl ester products to the corresponding carboxylic acids was observed. Heterocycles such as 6-bromoquinoline **2n** coupled smoothly (entry 13), but 2-chloropyridine gave complex reaction mixtures. Finally, bromobenzene provided very good yields of **3a**.[19]

Table 2. Pd-Catalyzed Reaction of **1a** with Aryl Halides[a]



entry	ArX		product	yield (%)[b]
1		**2b**	**3b**	66
2		**2c**	**3c**	89
3		**2d**	**3d**	72
4		**2e**	**3e**	88
5		**2f**	**3f**	71
6		**2g**	**3g**	96
7		**2h**	**3h**	53
8		**2i**	**3i**	68
9		**2j**	**3j**	67
10		**2k**	**3k**	74
11		**2l**	**3l**	60
12		**2m**	**3m**	96
13		**2n**	**3n**	82
14		**2o**	**3o**	63
15[c]		**2a**	**3a**	79

[a] Reactions run on 0.5 mmol **1a** at 100 °C for 15−18 h. No attempt was made to optimize for time. [b] Isolated yield of pure compound **3**. [c] Reaction run on 0.3 mmol of **1a**.

Variation of the thioacetate component **1** was also explored (Table 3). Electron-rich (entry 1), electron-poor

(14) (a) Segelstein, B. E.; Butler, T. W.; Chenard, B. L. *J. Org. Chem.* **1995**, *60*, 12. (b) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313. (c) Grushin, V. V. *Organometallics* **2000**, *19*, 1888.

(15) Although there is evidence that DPPF may be susceptible to aryl−aryl exchange (see: Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Sands, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618), Lee and coworkers (cf. ref 12) did not report any phenyl-incorporated side products.

(16) No attempts were made during our research to identify the precise time course of these events.

(17) See the Supporting Information for relevant ^{31}P NMR spectra.

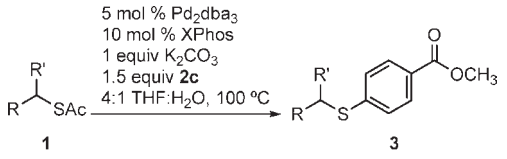
(18) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

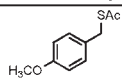
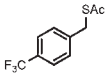
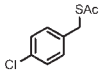
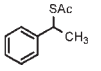
(19) Similar results were obtained with iodobenzene (61%); chlorobenzene gave much poorer yields (10%).

(20) (a) Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250. (b) Firouzabadi, H.; Iranpoor, N.; Gholinejad, M. *Adv. Synth. Catal.* **2010**, *352*, 119.

(entry 3), and sterically hindered (entry 5) thioacetates were tolerated. Thiobenzoates and thiopivalates were also effective (data not shown).

Table 3. Pd-Catalyzed Reaction of Thioacetates **1** with **2c**[a]



entry	RSAc		product	yield (%)[b]
1		**1b**	**3p**	90[c]
2		**1c**	**3q**	78
3		**1d**	**3r**	55
4		**1e**	**3s**	62
5		**1f**	**3t**	73

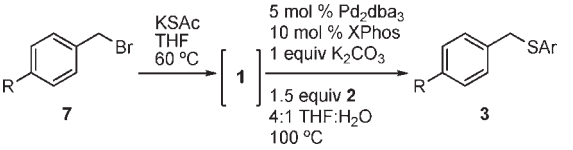
[a] Reactions run on 0.5 mmol of **1a** at 100 °C for 15–18 h. No attempt was made to optimize for time. [b] Isolated yield of pure compound **3**. [c] Based on 90% pure product.

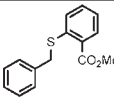
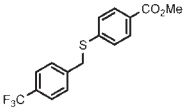
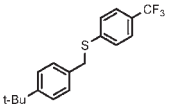
Thus far, we had demonstrated the ability to produce a variety of benzyl aryl thioethers through the palladium-catalyzed cross-coupling of aryl halides with thioacetates. We were interested to see if this procedure could be adapted to a more convenient one-pot protocol wherein an alkyl halide is reacted with potassium thioacetate, a readily available solid sulfur source, followed by immediate coupling in the same reaction vessel. Similar one-pot, three-component couplings of an aryl halide, an alkyl halide, and a sulfur source are known.[20]

Gratifyingly, treatment of bromide **7a** with potassium thioacetate (THF, 2 h, 60 °C) followed by in situ deprotection and cross-coupling **1c** with **2o** gave **3u** in 96% yield, highlighting the efficiency of both steps of this reaction. Table 4 shows several benzyl aryl thioethers prepared in good to excellent yields. Unfortunately, this reaction failed to give product with alkyl halides as starting material.

In summary, a method for synthesizing benzyl aryl thioethers from easy to handle and readily available

Table 4. One-Pot Formation of Benzyl–Aryl Thioethers[a]



entry	R	2	product	yield (%)[b]
1	H **7a**	**2o**		**3u** 96
2	CF_3 **7b**	**2c**		**3r** 44
3	*t*-Bu **7c**	**2f**		**3v** 65

[a] Reactions run on 0.5 mmol **7** with 1.1 equiv of KSAc at 60 °C for 2–3 h, followed by addition of remaining reagents and heating at 100 °C for 15–18 h. No attempt was made to optimize for time. [b] Isolated yield of pure compound **3**.

thioacetates has been developed. Deacylation and subsequent cross-coupling of thioacetates **1** can be achieved in the presence of mild aqueous base in up to 96% yield. In situ deprotection of thioacetates avoids the use of often odorous and unstable thiols in cross-coupling chemistry. As an even more streamlined procedure, we have demonstrated that a one-pot thioacetate formation/deacylation/cross-coupling sequence provides compounds **3** in moderate to excellent yields.

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Supporting Information Available. Full experimental details and characterization data for all compounds, ^{1}H NMR spectrum of **3a**-d_5, and ^{31}P NMR spectra for aryl–aryl transfer reaction studies. This material is available free of charge via the Internet at http://pubs.acs.org.