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Palladium-Catalyzed Cross-Coupling of 2-Aryl-1,3-dithianes

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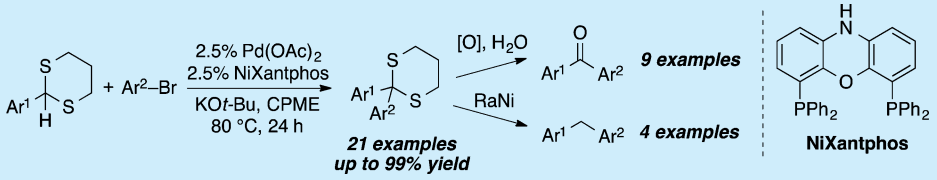
Supporting Information



ABSTRACT: Palladium-catalyzed cross-coupling of aryl bromides with 2-aryl-1,3-dithianes is described. This methodology takes advantage of the relatively acidic benzylic proton of the dithiane, allowing it to act as a competent, polarity-reversed transmetalation reagent. This unique approach affords the ability to employ an orthogonal deprotection strategy, and practical routes to both diaryl ketones and diarylmethanes are illustrated. Cross-coupling of a range of aryl dithianes with aryl bromides, including scope and current limitations, is presented.

Corey and Seebach first reported that 1,3-dithiane reagents could be used as acyl anion equivalents in 1965.[1] When dithianes reacted with an equivalent of *n*-butyllithium, the corresponding anions could be quenched with various electrophiles including primary and secondary alkyl halides, ketones, aldehydes, esters, carbon dioxide, and acyl chlorides. Since this seminal report, these versatile reagents have been widely utilized in synthesis as a reversed polarity synthon (Figure 1).[2] For example, Smith and co-workers developed anion relay chemistry relying on the nucleophilic character of the dithiane.[3]

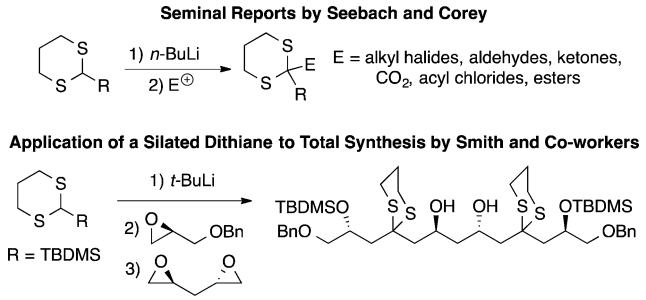


Figure 1. Umpolung reactivity of 1,3-dithianes.

Though this reactivity has been exploited over the years, dithiane nucleophiles as transmetalation reagents in cross-coupling reactions are conspicuously absent from the literature. On one hand, extending known transition-metal-catalyzed cross-coupling conditions to 1,3-dithiane derivatives should be an obvious one (Figure 2). With a pK_a of 30.7 (in DMSO), 2-phenyl-1,3-dithiane[4] is essentially as acidic as, for example, the α proton of ethyl acetate[5] (29.5, DMSO) or aniline[6] (30.6, DMSO). Palladium-catalyzed α-arylation of esters has been widely exploited,[7] and the C–N cross-coupling Buchwald–Hartwig reaction has been so thoroughly developed and subsequently utilized to be considered a routine laboratory

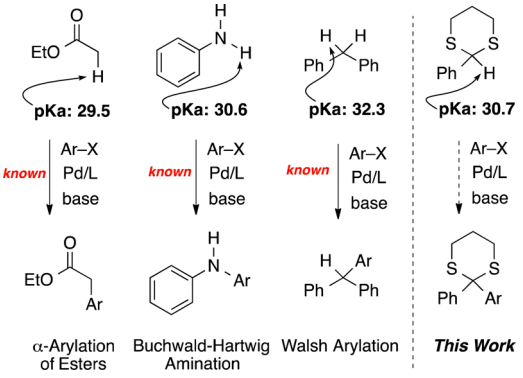


Figure 2. The pK_a trends of transmetalation reagents in cross-coupling reactions.

transformation.[8] Recently, Walsh and co-workers have even used the less activated diphenylmethane (pK_a 32.3, DMSO[9]) as a transmetalation reagent in Pd-catalyzed cross-coupling reactions.[10]

On the other hand, metal catalysts—especially palladium—can be sensitive to sulfur and susceptible to catalyst poisoning.[11] Yet, given the right catalyst environment, palladium-catalyzed cross-couplings proceed without difficulty in the presence of pendant thioethers.[12] Furthermore, C–S bond formation can be accomplished via cross-coupling that requires the intermediate complex with a Pd–S bond to be formed.[13]

Our group's interest in polarity-reversed cross-coupling chemistry arose from our and others' recent work using acylsilanes as cross-coupling reagents in palladium-catalyzed cross-coupling reactions.[14] At a preparative scale, the most

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straightforward synthesis of acylsilanes requires three steps from commercially available aldehydes.[15] While the first two steps are robust and high yielding, the final synthetic step is touchy at best due to the labile C(sp^2)−Si bond. This limits the modes of oxidative cleavage/hydrolysis to the acylsilane, and the unfortunate result is the need to use superstoichiometric mercury salts, followed by chromatographic purification of the crude reaction mixture. Ultimately, it is the most reliable route, as it leaves the C−Si bond intact where other known methods for dithiane deprotection[16] show a propensity to over oxidize to the carboxylic acid during hydrolysis (Figure 3).

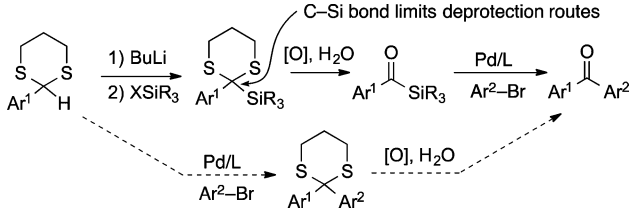


Figure 3. Streamlined route to diaryl ketones utilizing 1,3-dithianes.

It did not escape our notice, however, that to synthesize the acylsilanes, a carbon center with the desired, reversed-polarity characteristic has already been generated ***two steps prior***! If instead of completing the synthesis of the acylsilane, we intercepted the dithiane anion under cross-coupling conditions, we hypothesized that we could develop a novel methodology[17] that is more atom-economical,[18] requires fewer synthetic steps, and affords orthogonal dithiane deprotection strategies.

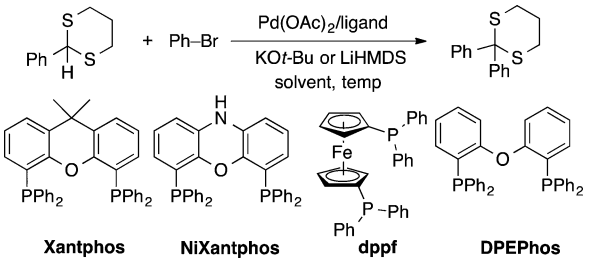
Initial reaction optimization focused first on bidentate phosphine ligands, as we hypothesized the palladium should be less susceptible to sulfur poisoning. Indeed, bisphosphines are routinely employed when carrying out palladium-catalyzed C−S bond formation.[19] Thus, our model reaction sought to couple 2-phenyl-1,3-dithiane with bromobenzene using 5% $Pd(OAc)_2$ and 10% of various phosphine ligands.

Due to the moderate acidity at the benzylic position, our initial optimization utilized LiHMDS in THF. At 60 °C, dppe and dppp showed no reactivity (Table 1, entries 3 and 4), though both dppf and DPEPhos led to some of the desired transformation (Table 1, entries 5 and 6). Interestingly, using the bidentate Xantphos ligand afforded none of the desired coupling,[20] though using the closely related NiXantphos led to complete consumption of both starting materials and quantitative conversion to the desired product after 24 h. It has been shown that under the basic reaction conditions, NiXantphos is likely deprotonated, leading to a very electron-rich palladium center.[21] Additionally, van Leeuwen and co-workers disclosed that NiXantphos has both a larger bite angle and is more flexible than Xantphos.[22] Investigations are ongoing in our lab to try to ascertain which of these phenomena, if either, leads to the observed difference in reactivity.

Our optimized set of conditions employs 2.5% $Pd(OAc)_2$ with 2.5% NiXantphos in CPME and uses 3.0 equiv of KO*t*Bu. Allowing the reaction to age at 80 °C for 24−48 h effected complete conversion and moderate to good isolated yields of a range of 2,2-diaryl-1,3-dithianes (Table 2).

A range of aryl bromides was shown to engage in this protocol, affording the cross-coupled product in fair to excellent yields. The reaction tolerated the cross-coupling of aryl bromide in the presence of aryl chlorides on either coupling

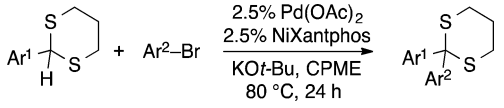
Table 1. Reaction Optimization[a]



entry	ligand	base	solvent	*t* (°C)	conv[b] (%)
1	none	LiHMDS	dioxane	60	0
2	PPh_3	LiHMDS	dioxane	60	0
3	dppe	LiHMDS	dioxane	60	0
4	dppp	LiHMDS	dioxane	60	0
5	dppf	LiHMDS	dioxane	60	44
6	DPEPhos	LiHMDS	dioxane	60	36
7	Xantphos	LiHMDS	dioxane	60	0
8	NiXantphos	LiHMDS	dioxane	60	100
9[c]	NiXantphos	LiHMDS	dioxane	60	100
10	NiXantphos	KO*t*Bu	dioxane	60	46
11	NiXantphos	KO*t*Bu	THF	60	53
12	NiXantphos	KO*t*Bu	toluene	60	4
13	NiXantphos	KO*t*Bu	CPME	60	58
14	NiXantphos	KO*t*Bu	CPME	80	100
15[d]	NiXantphos	KO*t*Bu	CPME	80	100

[a]1.0 mmol scale, 0.2 M, 2 equiv of LiHMDS or 3 equiv of KO*t*Bu, 5% $Pd(OAc)_2$, 10% ligand. [b]Liquid chromatography area percent. [c]5% $Pd(OAc)_2$, 5.0% NiXantphos. [d]2.5% $Pd(OAc)_2$, 2.5% NiXantphos.

Table 2. Cross-Coupling Aryl Bromides with 2-Aryl-1,3-Dithianes[a]



entry	Ar^1	Ar^2	yield[b] (%)
1	C_6H_5	C_6H_5	81
2	4-$MeSC_6H_4$	4-FC_6H_4	72
3	2-naphthyl	C_6H_5	65
4	C_6H_5	4-$MeOC_6H_4$	75, 83[c]
5	4-ClC_6H_4	4-$MeOC_6H_4$	86
6	4-$MeSC_6H_4$	4-$MeOC_6H_4$	99
7	2-naphthyl	4-$MeOC_6H_4$	89
8	4-FC_6H_4	4-$MeOC_6H_4$	83
9	3-$MeOC_6H_4$	4-$MeOC_6H_4$	72[c]
10	3,4,5-$(MeO)_3C_6H_2$	3-MeC_6H_4	81
11	3,4,5-$(MeO)_3C_6H_2$	4-MeC_6H_4	74
12	3,4,5-$(MeO)_3C_6H_2$	4-FC_6H_4	96
13	3,4,5-$(MeO)_3C_6H_2$	4-ClC_6H_4	90
14	3,4,5-$(MeO)_3C_6H_2$	4-*t*-BuC_6H_4	72[c]
15	3,4,5-$(MeO)_3C_6H_2$	2-naphthyl	61
16	3,4,5-$(MeO)_3C_6H_2$	4-$OCF_3C_6H_4$	72[c]
17	3,4,5-$(MeO)_3C_6H_2$	6-bromoquinoline	30[c]
18	3,4,5-$(MeO)_3C_6H_2$	3-bromopyridine	6
19	4-MeC_6H_4	4-$MeOC_6H_4$	67[d]
20	3,4,5-$(MeO)_3C_6H_2$	C_6H_5	63
21	4-Cl	4-BrC_6H_4	71[e]

[a]1.0 mmol scale, 0.2 M, 3 equiv KO*t*Bu. [b]Isolated yield after column chromatography. [c]48 h reaction time. [d]The aryl iodide (1.2 equiv, 60 °C) was used. [e]From 1,4-dibromobenzene.

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reagent (Table 2, entries 5 and 13). When a full equivalent of 1,4-dibromobenzene is used, only a single coupling is observed (via crude GC). An attempt to engage both electrophilic sites by adding only 0.5 equiv led to a messy reaction mixture, and still none of the disubstituted product was observed via GC or ^{1}H NMR of the crude reaction mixture.

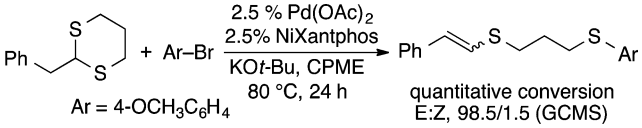
The cross-coupling proceeded smoothly with both moderately electron-rich and electron-poor partners, though when strong electron-withdrawing groups were a part of either the aryl bromide or the dithiane, reactivity was attenuated. Reactions run with a nitro, nitrile, or trifluoromethyl functionality as part of either of the coupling partners provided none of the desired products.

Additional initial limitations to this methodology include the inability to engage with sterically demanding aryl halides; for example, 2-bromotoluene or 2-bromoanisole showed no conversion to the desired diaryl dithianes. While both 3-bromopyridine and 6-bromoquinoline provided the expected products, the introduction of the electron-poor pyridine ring led to low isolated yields of 6 and 30%, respectively. Repeated attempts were made to use phenyl triflate in lieu of the bromide, though each was met with no observed cross-coupling. Research into improving these current limitations is ongoing.

Aryl iodides could be used in place of aryl bromides (Table 2, entry 19), though we found that direct application of the general procedure consumed the 4-iodoanisole without complete conversion of the aryl dithiane. However, decreasing the temperature to 60 °C and using a slight excess of the iodide afforded complete conversion of both starting materials and an 67% isolated yield of the title compound.

Interestingly, when this methodology was applied to 2-benzyl-1,3-dithiane, a tandem elimination/ring opening followed by a Pd-catalyzed C−S bond formation was observed (Scheme 1). Initial data indicate that this new reaction proceeds

Scheme 1. Reaction with 2-Benzyl-1,3-dithiane



with a high degree of *trans* specificity. Further investigations into this ring opening are underway, and the results will be reported in due course.

Our putative mechanism for this new transformation conforms well to other cross-coupling mechanisms. In particular, we suspect that the transmetalation/ligand exchange step is similar to α-carbonyl arylation, whereby precoordination to the catalytic center of the extant nucleophile (here, sulfur) increases the acidity of the C2 carbon of the dithiane, assisting in transmetalation. We have begun kinetic studies in order to more fully understand this mechanism (Figure 4).

Differential deprotection of the diaryl dithianes afforded benzophenones or diarylmethanes. After cross-coupling, the crude reaction mixture could be taken on to the next step directly where the dithiane was oxidatively hydrolyzed[23] to afford the substituted benzophenones in good yield over two steps (Table 3). Alternatively, the crude reaction mixture could be taken up in ethanol and refluxed overnight in the presence of Raney nickel to afford diarylmethanes in good yield. The flexibility of the removal of the dithiane to access two important

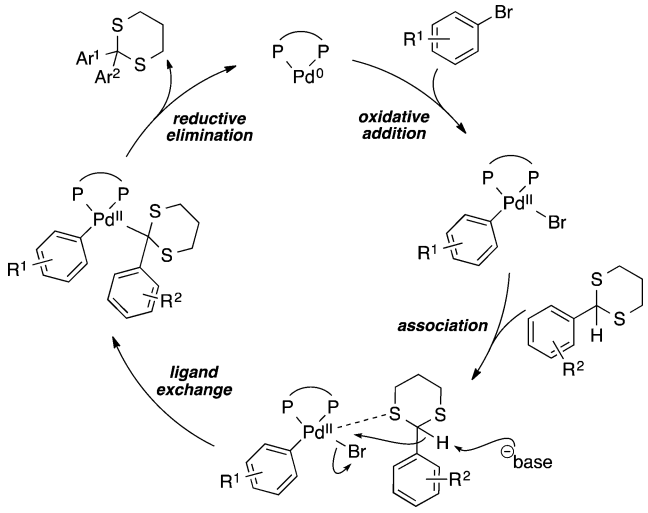
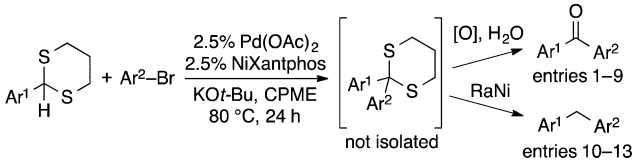


Figure 4. Putative catalytic cycle.

Table 3. Synthesis of Benzophenones and Diarylmethanes via Two-Step, One Pot Procedures



entry	Ar^1	Ar^2	yield[b] (%)
	benzophenones[a]		
1	4-FC_6H_4	4-$MeOC_6H_4$	66
2	3-MeC_6H_4	4-$MeOC_6H_4$	52
3	4-ClC_6H_4	4-$MeOC_6H_4$	55
4	4-$MeSC_6H_4$	4-$MeOC_6H_4$	65[c]
5	3,4,5-$(MeO)_3C_6H_2$	4-$MeOC_6H_4$	72
6	3,4,5-$(MeO)_3C_6H_2$	4-FC_6H_4	66
7	3,4,5-$(MeO)_3C_6H_2$	4-ClC_6H_4	40
8	3,4,5-$(MeO)_3C_6H_2$	4-*t*-BuC_6H_4	41
9	3-$MeOC_6H_4$	4-$MeOC_6H_4$	53
	diarylmethanes[a]		
10	3-$MeOC_6H_4$	4-$MeOC_6H_4$	54
11	C_6H_5	4-$MeOC_6H_4$	50
12	3-MeC_6H_4	4-$MeOC_6H_4$	53
13	3,4-$(OCH_2O)C_6H_3$	3-MeC_6H_4	38

[a]1.0 mmol scale. [b]Two-step isolated yield after column chromatography. [c]Trace amount of the oxidized methyl thioether was detected in the crude ^{1}H NMR.

compounds classes should make this an attractive methodology in small molecule synthesis.

In conclusion, we have reported the first palladium-catalyzed cross-coupling of 2-aryl-1,3-dithianes with a range of aryl bromides using a $Pd(OAc)_2$/NiXantphos catalyst system. After cross-coupling, the pendant dithiane can either be cleaved with Raney nickel to afford diarylmethanes or hydrolyzed to afford substituted benzophenones in good yields. Work is being pursued to expand the scope of this reaction to include heteroaryl bromides and aryl and heteroaryl triflates. Finally, we have begun to examine the interesting tandem ring opening, C−S bond formation encountered when employing 2-benzyl-1,3-dithianes.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all compounds. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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