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Cleavage of the C(O)−S Bond of Thioesters by Palladium/Norbornene/Copper Cooperative Catalysis: An Efficient Synthesis of 2-(Arylthio)aryl Ketones

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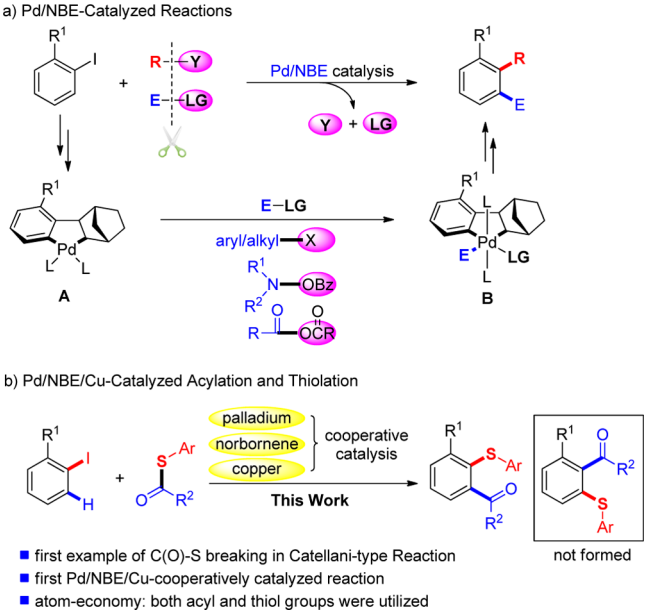
Supporting Information

ABSTRACT: A Pd/norbornene/Cu cooperative catalysis for the efficient synthesis of 2-(arylthio)aryl ketones from aryl halides and thioesters has been developed. The first example of cooperative catalysis by palladium, norbornene, and copper, wherein the C(O)−S bond of thioesters is cleaved by a Pd^{II} palladacycle with the assistance of CuI, has been observed.

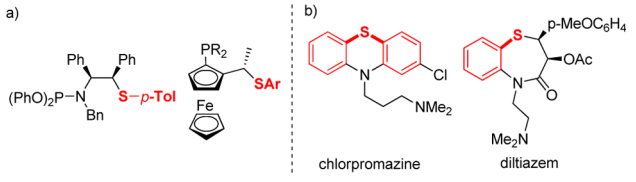
Transition-metal-catalyzed C−C and C−heteroatom bond-forming reactions are among the most important achievements in modern synthetic organic chemistry. Among them, palladium/norbornene (NBE)-catalyzed ortho C−H functionalization is a powerful and mechanistically interesting process for the construction of 1,2,3-substituted arenes. The reaction was discovered by Catellani in 1997,[1] and significant developments were achieved in the last one and a half decades by the groups of Lautens, Catellani, and others.[2,3] It is generally believed that the key intermediate of this Pd/NBE-catalyzed reaction is palladacycle **A**, which reacts with proper electrophiles (**E**−**LG**) to give Pd^{IV} intermediate **B** (Scheme 1a).[4] By the use of functionalized aryl or alkyl halides and different termination reagents (**R**−**Y**), a number of polysubstituted arenes with divergent functionalities have been synthesized (Scheme 1a). Taking advantage of the palladium/NBE strategy, the Yu and Dong groups successfully realized chelation-directed meta-selective C−H functionalization reactions.[5] Furthermore, the feasibility of this protocol resulted in successful applications in the synthesis of natural products, including (+)-linoxepin, goniomitine, aspidospermidine, and rhazinal.[6] However, early studies of this reaction mostly focused on the development of versatile termination reagents, and the electrophiles (**E**−**LG**) were limited to aryl or alkyl halides. Recently, the scope of electrophiles was broadened to include *O*-benzoyl hydroxylamines and acid anhydrides (or acid chlorides), which react with palladacycle **A** to give an array of anilines and aryl ketone derivatives (Scheme 1a).[7]

It is reasonable to hypothesize that a variety of electrophiles might undergo the oxidative addition reaction with palladacycle **A** to afford ortho-functionalized products under proper reaction conditions. However, until now only three major types of electrophiles—organic halides, *O*-benzoyl hydroxyamines, and acid anhydrides—have been successfully applied to Catellani-type reactions.[3a,8] On the other hand, aryl sulfides are important intermediates and ligands in organic synthesis.[9] They are also represented in biologically and pharmaceutically active molecules (Scheme 2).[10] Given the importance of aryl sulfides, we reasoned that the C(O)−S bond of thioesters might be cleaved by palladacycle **A** to give 2-(arylthio)aryl ketones in an economical transformation.[11,12] However, the following challenges in this process were anticipated: (1) identification of a catalyst that could activate the C(O)−S bond and be compatible with Pd/NBE catalyst system and (2) controlling the reactivity of the thioesters such that they are activated for a reaction with palladacycle **A** while remaining inert to Pd^0. Herein we report our efforts toward the cleavage of the C(O)−S bond of thioesters for

Scheme 1. Modes for Pd/NBE-Catalyzed Reactions



Scheme 2. Aryl Sulfides in Ligands and Pharmaceutical Molecules



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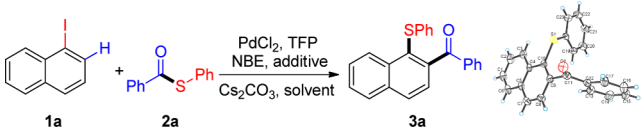
the ortho C−H acylation and ipso thiolation of iodoarenes and the first examples of palladium/NBE/copper cooperative catalysis (Scheme 1b).

Our initial investigation began with 1-iodonaphthalene (**1a**) and *S*-phenyl benzothioate (**2a**) in the presence of $PdCl_2$, NBE, and tris(2-furyl)phosphine (TFP) in dioxane. To our delight, we did isolate the desired product **3a** in 10% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



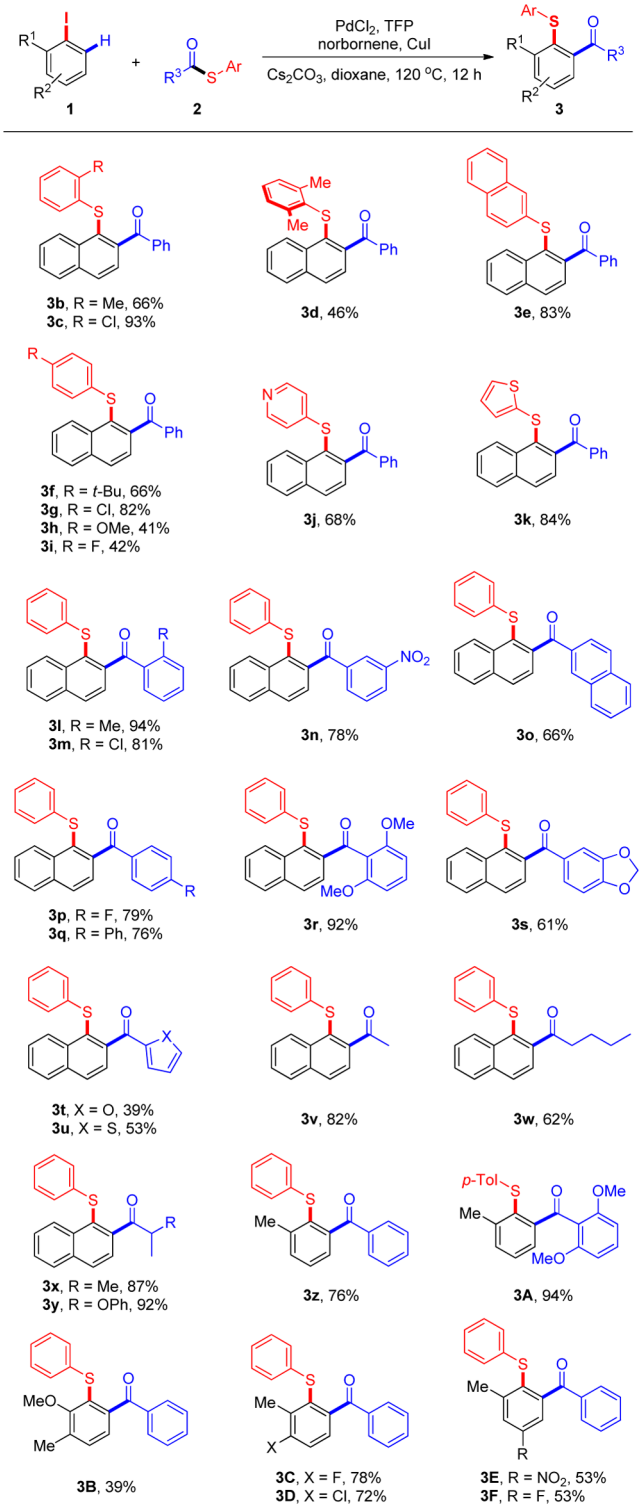
entry	Pd	additive	solvent	yield (%)[b]
1	$PdCl_2$	–	dioxane	10
2	$PdCl_2$	CuOAc	dioxane	22
3	$PdCl_2$	CuTC	dioxane	81
4	$PdCl_2$	CuCl	dioxane	47
5	$PdCl_2$	CuBr	dioxane	86
6	$PdCl_2$	CuI	dioxane	85
7	$PdCl_2$	CuI	MeCN	64
8	$PdCl_2$	CuI	DCE	45
9	$PdCl_2$	CuI	toluene	56
10	$PdCl_2$	CuI/1,10-Phen	dioxane	–
11	$Pd(OAc)_2$	CuI	dioxane	38
12[c]	$Pd_2(dba)_3$	CuI	dioxane	78
13	$PdCl_2$	$AgBF_4$	dioxane	36
14	$PdCl_2$	$Au(PPh_3)Cl$	dioxane	87

[a]The reactions were conducted with **1a** (0.20 mmol), **2a** (0.30 mmol), Pd (10 mol %), TFP (25 mol %), and additive (20 mol %) in the indicated solvent at 120 °C for 12 h under a nitrogen atmosphere. [b]Isolated yields. [c]5 mol % $Pd_2(dba)_3$ was used.

The regioselectivity of the product was unambiguously confirmed by single crystal X-ray analysis.[13] These results encouraged us to pursue further optimization. After the efforts to improve the yield by screening phosphine ligands, bases, and solvents failed, our attention turned to a search for some potential activators to accelerate the C(O)−S bond cleavage. The addition of 20 mol % CuOAc gave an improved yield of 22% (entry 2). We were pleased to see that the yield of **3a** increased dramatically to 81% when copper(I) thiophene-2-carboxylate (CuTC) was used as the additive (entry 3). The screening of copper salts and solvents found that CuBr and CuI in dioxane gave the best isolated yields (entries 4−9). The addition of 1,10-phenanthroline resulted in complete inhibition of the reaction (entry 10). In the examination of the palladium source, it was found that $Pd(OAc)_2$ gave inferior results and that the reaction with $Pd_2(dba)_3$ worked with marginally lower efficiency (entries 11 and 12). Other group 11 metal salts, such as $AgBF_4$ and $Au(PPh_3)Cl$ were also tested as additives, and $Au(PPh_3)Cl$ showed equal efficiency as CuI and CuBr (entries 13 and 14).

With the optimum conditions in hand, various 2-(arylthio)-aryl ketones could be synthesized in a straightforward and efficient manner (Table 2). The reactions of 2-methylphenyl and 2-chlorophenyl thioesters delivered the corresponding products **3b** and **3c** in moderate to excellent yields.[14] Notably, **3d** with a sterically hindered 2,6-dimethylphenylthiol moiety was isolated in 46% yield. *β*-Naphthylthiol ether **3e** was also synthesized efficiently. Studies of electronic effects by varying the para substitutent on the phenylthiol moiety indicated that

Table 2. Substrate Scope[a]



[a]The reaction was conducted with iodide (0.20 mmol), thioester (0.30 mmol), $PdCl_2$ (10 mol %), TFP (25 mol %), and CuI (20 mol %) in dioxane at 120 °C for 12 h. For details, see the Supporting Information.

both strong electron-donating (methoxy) and electron-withdrawing (F) groups decreased the efficiency of the reaction (**3h** and **3i** in comparison with **3f** and **3g**). Heteroaryl thioesters such as *S*-pyridin-4-yl benzothioate and *S*-thiophen-2-yl benzothioate were compatible components, and the corresponding

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reactions gave **3j** and **3k** in 68% and 84% yield, respectively. Aliphatic thioesters were not good substrates, and complicated mixtures were detected. Further studies of the effect of the substituent on the aryl acyl moiety were carried out. There was no significant effect of substituents at the ortho, meta, and para positions, and the reactions gave the corresponding products **3l**–**q** in valuable yields; notably, the electron-deficient nitro-substituted product **3n** was isolated in 78% yield. The reactions with electron-donating substituents on the phenyl ring worked uneventfully and gave satisfactory yields (**3r** and **3s**). However, replacing the phenyl ring with a 2-furyl or 2-thiophenyl group caused the yield to drop significantly (**3t** and **3u**). To our delight, the reactions with enolizable aliphatic acid-derived thioesters, including α-branched derivatives, worked smoothly and afforded the products in decent to excellent yields (**3v**–**y**). This is a great improvement in comparison with the previous Pd/NBE-catalyzed ortho acylation reaction, which provided poor yields with aliphatic acyl groups.[7e,f] It is worth noting that α-phenoxy-functionalized product **3y** could be formed in excellent yield (92%).

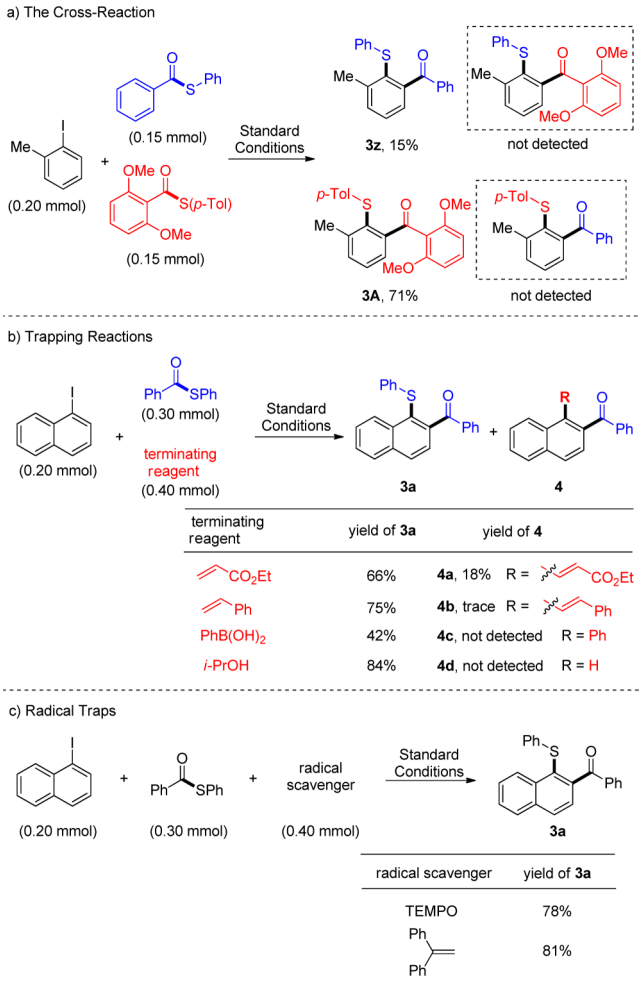
Studies regarding the scope of aryl halides were also carried out. The reactions of 2-methyl iodobenzenes performed smoothly to give the products in decent to excellent yields (**3z**, **3A**, **3C**, and **3D**), while the reaction of 2-methoxy-substituted iodobenzene afforded a decreased yield (**3B**). Iodobenzenes with electron-withdrawing groups such nitro and fluoro were also compatible, and the reactions furnished the corresponding sulfides in moderate yields (**3E** and **3F**).

A cross-reaction of **1a** with *S*-phenyl benzothioate and *S*-(*p*-tolyl) 2,6-dimethoxybenzothioate was conducted under the standard reaction conditions. It was interesting to find that *no cross-product was detected* (Scheme 3a). Furthermore, **3A** was isolated in 71% yield while **3z** was formed in only 15% yield, indicating that *S*-(*p*-tolyl) 2,6-dimethoxybenzothioate was more reactive than *S*-phenyl benzothioate. When an extra 2 equiv of ethyl acrylate was added, sulfide **3a** was formed dominantly (66%) along with **4a** (18%). However, only a trace amount of styrene-terminated product **4b** could be detected when 2 equiv of styrene was added (Scheme 3b). Moreover, no corresponding coupling product **4c** or reductive product **4d** could be detected in the presence of phenylboronic acid or isopropanol (Scheme 3b). The addition of a radical scavenger such as TEMPO or 1,1-diphenylethene only slightly lowered the yield of **3a** (Scheme 3c). Thus, a radical pathway for the reaction appears to be unlikely.

According to studies of the Liebeskind–Srogl reaction, the Cu^{I} salt may serve as a C(O)–S bond activator through coordination to the sulfur center.[12] However, mechanistic details of this reaction, particularly in regard to the role of Cu^{I}, are not clear and are currently under investigation.[15]

In conclusion, we have reported a Pd/NBE/Cu-catalyzed ortho C–H acylation and ipso thiolation reaction of aryl halides involving cleavage of the C(O)–S bond of thioesters. The reaction proceeds in an atom-economical way, as both the acyl and thiol groups are incorporated into the aryl ring. This is the first example in palladium/norbornene catalysis where a Lewis acid (CuX) assists the oxidative addition of a Pd^{II} palladacycle with electrophiles. This method provides a new and efficient route for the synthesis of 2-(arylthio)aryl ketones.

Scheme 3. Control Experiments



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02495.

Experimental procedures, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for new compounds (PDF)
Crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) CCDC 1456693 contains the supplementary crystallographic data for compound **3a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(14) Byproducts, including direct thiolation products, were detected, which accounted for the relatively lower yields in some cases. For details, see the Supporting Information.

(15) We appreciate one of the referees' suggestion to remove the conventional catalytic cycle for Pd/NBE catalysis, and allowing further mechanistic studies to be performed subsequently.

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