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Aryl Methyl Sulfides as Substrates for Rhodium-Catalyzed Alkyne Carbothiolation: Arene Functionalization with Activating Group Recycling

Joel F. Hooper, Adrian B. Chaplin, Carlos González-Rodríguez, Amber L. Thompson, Andrew S. Weller,* and Michael C. Willis*

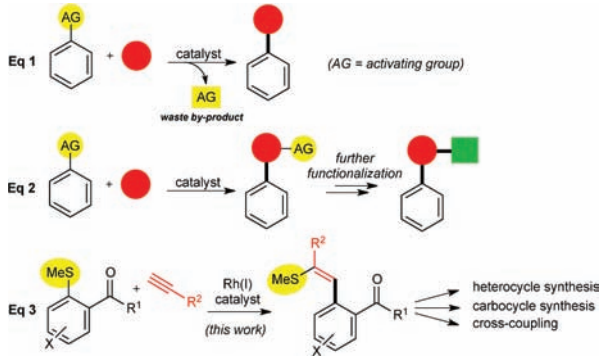
Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, U.K.

Supporting Information

ABSTRACT: A Rh(I)-catalyzed method for the efficient functionalization of arenes is reported. Aryl methyl sulfides are combined with terminal alkynes to deliver products of carbothiolation. The overall process results in reincorporation of the original arene functional group, a methyl sulfide, into the products as an alkenyl sulfide. The carbothiolation process can be combined with an initial Rh(I)-catalyzed alkene or alkyne hydroacylation reaction in three-component cascade sequences. The utility of the alkenyl sulfide products is also demonstrated in simple carbo- and heterocycle-forming processes. We also provide mechanistic evidence for the course of this new process.

The ubiquitous nature of aromatic and heteroaromatic groups in pharmaceuticals and agrochemicals and the requirement to manipulate these aromatic units in synthetically useful ways have resulted in the development of an enormous range of synthetic methods.[1] Some of the most useful of these are based on transition-metal catalysis, with those based on Pd catalysts arguably the most widely employed.[2] Despite the utility of these methods, the majority employ an activating group (AG), most usually a halide or sulfonate, to control both the reactivity and regiochemistry of the reactions. Thus, all of these transformations generate AG-derived waste byproducts (eq 1 in Scheme 1). The recent development of methods based on C−H functionalization (or activation) go some way toward addressing these limitations but as yet are not general transformations.[3] In a recent elegant report, Newman and Lautens demonstrated that in specific cases it is possible to reincorporate an iodine atom following C−C bond formation using Pd catalysis (eq 2 in Scheme 1; AG = I).[4,5] In a complementary approach, we now report chemistry based on the activation of simple methyl aryl sulfides using Rh(I) catalysis in which an intermolecular carbothiolation process delivers alkenyl sulfide products. The transformation results in reincorporation of the original methyl sulfide AG into the products in the form of an alkenyl sulfide unit, effectively recycling the AG, which can than be used for further transformations (eq 3 in Scheme 1). This method achieves bond activation and formation under mild conditions, has good functional group tolerance, and displays orthogonal reactivity to the more usual Pd-based coupling reactions. In addition to documenting the scope of this new process, we also provide evidence for the mechanism that underpins this novel transformation.

Scheme 1



When selecting a basic reaction framework on which to develop an AG-recycling strategy, we chose to focus on addition-type processes instead of cross-coupling systems based on transmetalation, as one of our aims was to deliver a completely atom-economic protocol. We also wanted to employ an AG that would complement those used in traditional arene functionalization chemistry. We therefore chose to focus not on halide or sulfonate groups but on simple aryl methyl sulfides (ArSMe). Although *activated* C−S bonds can be cleaved by a variety of transition-metal catalysts,[6] examples involving the activation of simple aryl sulfides are significantly more limited. For example, while unstrained aryl alkyl sulfides were employed in some early examples of Ni-catalyzed cross-coupling reactions with Grignard reagents,[7] no cases of simple aryl alkyl sulfides taking part in addition-type processes are known.[8] In addition, methyl sulfides were attractive substrates because of their general chemical robustness, a feature not shared by a number of S-based functional groups used in known carbothiolation reactions.[6]

We selected the coupling of ArSMe **1a** and phenylacetylene (**2a**) to test our proposed methodology, and Rh(I)−DPEphos-derived complexes proved to be efficient catalysts for the targeted transformation. For example, under hydroacylation-like conditions,[9] the complex [Rh(DPEphos)(nbd)][BAr^F_4] [nbd = norbornadiene; Ar^F = 3,5-$(CF_3)_2C_6H_3$] promoted the union of **1a** and **2a** to generate alkenyl sulfide **3a** in only 5% yield (Table 1, entry 1), but this was increased to 90% by

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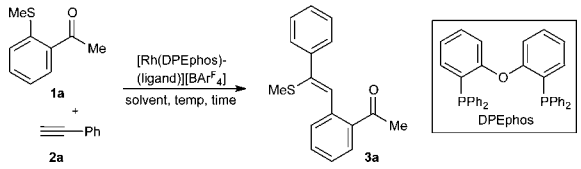
Table 1. Optimization of the Coupling of 1a and 2a[a]



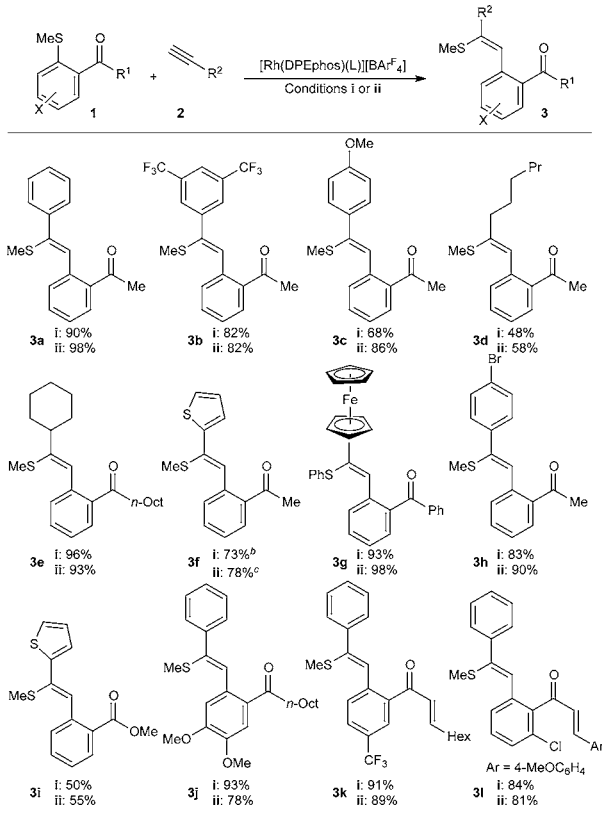
entry	ligand	solvent	temp (°C)	time (h)	yield (%)[b]
1	nbd	acetone	55	30	5
2	nbd	DCE	80	16	70
3	nbd	toluene	110	4	74
4	nbd	*o*-xylene	130	1	90
5	*o*-xylene	acetone	55	5	37
6	*o*-xylene	*o*-xylene	130	0.25	98
7	*o*-xylene	*o*-xylene	60	4.5	98
8	*o*-xylene	*o*-xylene	25	30	95

[a]Conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), catalyst (5.0 mol %). [b]Isolated yields.

variation of solvent and reaction temperature (entries 2−4). Importantly, the alkenyl sulfide products were generated as single geometric isomers, suggesting a stereoselective addition process.[8,10,11] We postulated that substitution of the nbd ligand was one limiting factor in turnover. Exchange for the more labile *o*-xylene gave the complex [Rh(κ^2-*P*,*P*-DPEphos)(η^6-*o*-xylene)][BAr$^F_4$] (**A**) (see Scheme 2 for the X-ray structure), which delivered a more efficient process at a number of different temperatures (entries 5−8). An important observation from a practical perspective is that the complex incorporating xylene as a ligand, **A**, is bench-stable and easy to handle.

The optimized conditions developed for the coupling of **1a** and **2a** were then applied across a varied range of substrates (Table 2). Both the nbd and *o*-xylene catalysts were evaluated across all substrates, with reaction temperatures and times adjusted accordingly. The process proved to be broad in scope, tolerating a variety of steric and electronic changes to both reaction partners. For example, products **3b** and **3c** demonstrate the ability of the arylalkyne to bear either electron-withdrawing or -donating aryl substituents. Alkyl-substituted alkynes could also be employed (**3d, 3e**). To demonstrate the ability of the process to tolerate alternative functionality, both 2-thienyl (**3f**) and ferrocenyl (**3g**) substituents were efficiently incorporated. Example **3g** also illustrates that phenyl sulfides can function as the AG. The final variation of the alkyne substrate (shown in product **3h**) is significant, as it demonstrates that bromo substituents can be tolerated on the arene ring; given the wide use of aryl bromides in Pd-catalyzed coupling chemistry, the benign nature of this group under the present reaction conditions holds promise for further manipulation of the products using complementary catalytic methods. A control experiment utilizing the para-disposed regioisomer of **1a** established that the present reaction system requires a carbonyl group positioned ortho to the methyl sulfide being activated (see discussion below). However, alteration of the type of carbonyl group is possible, as is variation of the remaining positions of the arene. For example, a methyl ester can be used in place of the original ketone (**3i**), as can a longer-chain (**3j**) or aryl (**3g**) ketone as well as an enone (**3k**). Electron-donating MeO substituents (**3j**) or an electron-withdrawing CF_3 group (**3k**) can also be readily introduced onto the arene ring. Finally, an aryl chloride-substituted product (**3l**) was efficiently produced, again demonstrating the ability of the methodology to tolerate substituents useful for further product modification. The reaction can

Table 2. Scope of the Rh(I)-Catalyzed ArSMe/Alkyne Carbothiolation Process[a]



[a]Conditions: **1** (1.0 equiv), **2** (2.0 equiv), catalyst (5.0 mol %). Isolated yields are shown. Conditions: (**i**) [Rh(DPEphos)(nbd)][BAr$^F_4$], 130 °C, *o*-xylene, 1 h; (**ii**) [Rh(DPEphos)(*o*-xylene)][BAr$^F_4$], 60 °C, *o*-xylene, 4−24 h (see the SI for details). [b]Reaction performed at 25 °C. [c]Reaction performed at 100 °C.

be performed on a preparatively useful scale; for example, **3a** was routinely prepared in >0.5 g (1.9 mmol) quantities. Under the present reaction conditions, it is not possible to employ internal alkynes or alkenes in the carbothiolation process.

With an aryl to alkenyl sulfide AG transfer in place, we next established the key mechanistic details of this new process using **A** as the precatalyst, probing the identities of the likely organometallic intermediates in the catalytic cycle using a series of both stoichiometric and catalytic experiments. The solid-state X-ray structure of **A** (Scheme 2) shows η^6-bound *o*-xylene and κ^2-*P*,*P*-DPEphos ligands, which is fully consistent with solution NMR data. **A** undergoes solvent arene exchange with *o*-xylene-d_{10} (first-order substitution, $t_{1/2}$ = 20 min), showing that the *o*-xylene is labile and provides access to the reactive [Rh(DPEphos)]$^+$ fragment.

In CD_2Cl_2, reaction of **A** with **1a** produces an equilibrium mixture of the isomeric complexes [Rh(*fac*-κ^3-*P*,*O*,*P*-DPEphos)(SMe)(σ-*C*,κ-*O*-$C_6H_4C(O)Me$)][BAr$^F_4$] (**C**) and [Rh(*mer*-κ^3-*P*,*O*,*P*-DPEphos)(SMe)(σ-*C*,κ-*O*-$C_6H_4C(O)Me$)][BAr$^F_4$] (**D**) alongside free *o*-xylene (298 K, **C**:**D** = 1.0:7.8). In *o*-xylene-d_{10}, a mixture of **A**, **C**, and **D** is established, the relative proportions of which change with temperature (298 K, **A**:**C**:**D** = 0.1:0.1:1.0; 333 K, **A**:**C**:**D** = 0.3:0.0:1.0). Characterization of **C** and **D** by NMR spectroscopy (CD_2Cl_2) and electrospray ionization mass spectrometry (ESI-MS)[12] suggested that both **C** and **D** are Rh(III) species arising from reversible[6g,13] C_{aryl}−S bond cleavage.[6a,14] Similar NMR data were obtained for the

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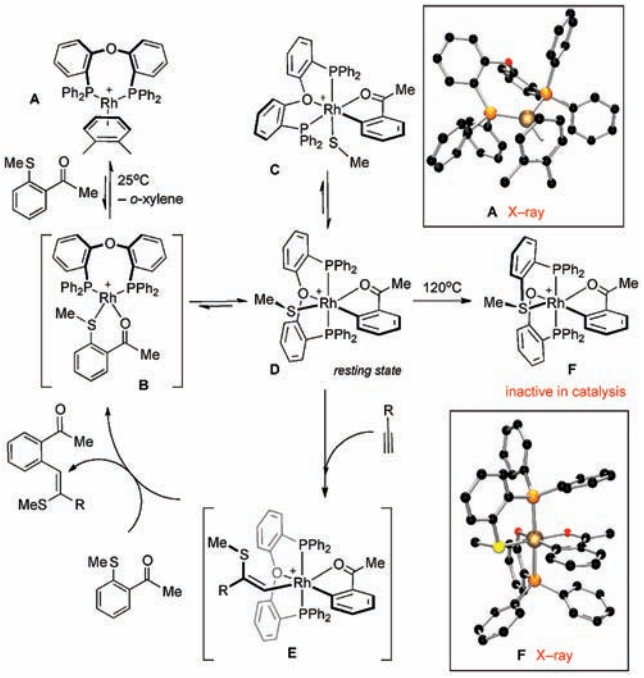
Scheme 2



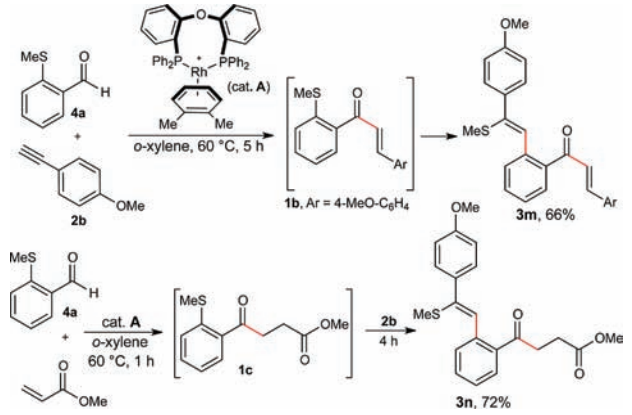
product of oxidative addition of the structurally similar aldehyde 2-(methylthio)benzaldehdye to $[Rh(DPEphos)]^+$,[9e] and related precursors,[15] to give acyl hydride complexes with chelated ArSMe ligands that are closely related to the structures suggested for **C** and **D**. We also showed that in these complexes the DPEphos ligand can act in a hemiliable manner,[16] suggesting that interconversion between **C** and **D** could occur via O-decoordination to access a conformationally flexible five-coordinate intermediate. The reaction between **A** and 4-(methylthio)acetophenone (the para isomer of **1a**) in *o*-xylene-d_{10} (298–333 K) resulted in no reaction, demonstrating the requirement that the carbonyl group be positioned ortho to the methyl sulfide in this system. Heating a mixture of **A**, **C**, and **D** with just the alkyne 1-bromo-4-ethynylbenzene (40 equiv, 333 K, 6 h) resulted in the formation of the expected product **3h**. **A** and **D** were also observed at the end of the reaction.[17]

On the basis of these observations, we suggest the catalytic cycle shown in Scheme 2. Addition of **1a** to **A** generates an equilibrium mixture of **A** and products resulting from Ar–S bond cleavage. Addition of alkyne then results in productive turnover by insertion and then reductive elimination, giving an overall carbothiolation of the alkyne.[8,18] We suggest that migration of SMe to the alkyne occurs first[11] (to form **E**), followed by reductive elimination of the vinyl and aryl groups; a similar sequence of events was delineated for the hydroacylation reaction of alkenes and *o*-SMe-substituted aromatic aldehydes.[9d] This sequence returns the reactive $[Rh(DPEphos)]^+$ fragment. During catalysis (5 mol % **A**, 333 K), sampling the reaction showed that **D** was the only significant organometallic species at all intermediate times, as observed by $^{31}P\{^1H\}$ NMR spectroscopy (xylene, 298 K), indicating that either alkyne insertion or reductive elimination of the product is the likely turnover-limiting step.

In the absence of alkyne,[12] extended heating of **A** with **1a** (1.5 equiv, 393 K) cleanly formed a new complex **F** (first-order conditions, $t_{1/2}$ = 60 min). NMR, ESI-MS, and single-crystal X-ray diffraction (XRD) analysis of **F** (Scheme 2) showed that C–O bond cleavage accompanied by C–S bond formation occurs in the DPEphos ligand to generate an aryl thioether and a chelating phosphine aryl oxide. As far as we are aware, this reactivity (i.e., C–O bond cleavage) has not been previously observed for DPEphos and presents a new and interesting deactivation pathway for this popular ligand. Related P–C cleavage in phosphine ligands is well-established as a deactivation pathway.[19] Complex **F** sits off-cycle and is not an active catalyst, as reacting isolated **F** under catalytic conditions resulted in no turnover. We suggest that a possible mechanism for the conversion of **D** to **F** is nucleophilic substitution by SMe at the C_{aryl}–O bond to afford a phenoxide and a new aryl thioether. This bond cleavage reaction in **D** is considerably slower than catalytic turnover with alkyne, and **D** is thus intercepted by alkyne faster than P–O cleavage occurs: at 393 K, catalysis (5 mol %) is complete in 15 min, while P–O bond cleavage takes 6 h to go to completion at high temperature.

In view of the close structural similarities of the catalysts in the present alkyne carbothiolation process and our earlier hydroacylation chemistry employing S-substituted aldehydes,[9,15] in addition to the mechanistic connections between the two transformations, the possibility of constructing hydroacylation/carbothiolation cascades was an attractive one. Scheme 3 shows two successful cascade processes. In the first

Scheme 3



example, *o*-MeS-aldehyde **4a** was combined with an excess of alkyne **2b** under the action of the complex $[Rh(DPEphos)(o\text{-xylene})][BAr^F{}_4]$; initial alkyne hydroacylation generated enone **1b** in situ, which then underwent C–S activation/alkyne insertion to deliver alkenyl sulfide **3m** in 66% overall yield. Alternatively, initial alkene hydroacylation could be employed: reaction of **4a** with methyl acrylate and the same Rh–DPEphos catalyst led initially to ketone **1c**, after which addition of alkyne **2b** afforded **3n** in 72% yield for the two-step, one-pot cascade process.

To demonstrate the utility of the developed AG-recycling strategy, we briefly explored the chemistry of the alkenyl sulfide products. For example, treatment of **3a** with aqueous Lewis acid conditions transformed it into the corresponding ketone **5**. Direct treatment of **5** with base resulted in intramolecular aldol condensation to form phenol **6** (Scheme 4). Alternatively, reaction of **3n** with ammonium acetate solution resulted in the direct formation of isoquinoline **7**. Since **3n** was prepared by an initial Rh(I)-catalyzed hydroacylation reaction, the ArSMe group was integral to three consecutive transformations: Rh(I)-catalyzed alkene hydroacylation (**4a** → **1c**), Rh(I)-catalyzed alkyne carbothiolation (**1c** → **3n**), and isoquinoline formation

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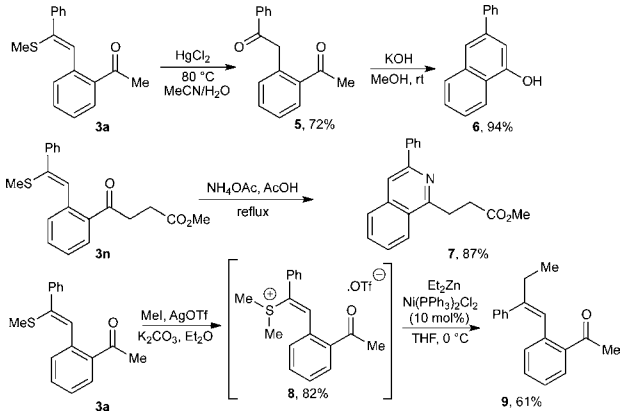
Scheme 4



(**3n** → **7**). Finally, conversion of **3a** to the corresponding sulfonium salt **8** and then reaction with Et_2Zn under Ni catalysis resulted in cross-coupling, leading to trisubstituted alkene **9**.[20,21]

In conclusion, we have developed a novel Rh(I)-catalyzed carbothiolation of alkynes using simple aryl methyl sulfides. The reaction is stereospecific, delivering single isomers of alkenyl sulfide products. Importantly, we have demonstrated that this new transformation is an example of AG recycling, in that the initial methyl sulfide AG is embedded in the alkenyl sulfide product, providing a versatile group for further synthetic transformations. Given the robust nature of the process (tolerance to temperature variation, scale, and incorporation into cascade processes), the broad substrate scope, and the ability to generate the bench-stable catalyst from simple and readily available components, we believe that this new reaction has the potential to find wide application in synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and reactions of **A** with excess alkyne. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

andrew.weller@chem.ox.ac.uk; michael.willis@chem.ox.ac.uk

Notes

The authors declare no competing financial interest.

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(21) The alkene geometry in compound **9**, resulting from an inversion, was unexpected. The geometries of the alkenes in both **3a** and **9** were established using NOE experiments. The geometry of the intermediate **8** was established using XRD (see the SI for details).