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Efficient ruthenium-catalysed S–S, S–Si and S–B bond forming reactions[†]

José A. Fernández-Salas, Simone Manzini and Steven P. Nolan*

 $[RuCl(PPh_3)_2(3-phenylindenyl)]$ (1) has been shown to be an efficient catalyst in thiol dehydrogenative coupling to give disulfides. Moreover, an efficient procedure for the preparation of silylthioethers and thioboranes is presented. Complex 1 demonstrated a great ability to catalyse the coupling of thiols with silanes and boranes under mild conditions with excellent results (turnover number up to 200).

Organosulfur compounds have been used extensively in synthetic organic chemistry¹ and their transformations have always been of interest, especially the oxidation of thiols into disulfides. Disulfides play very important roles in both nature² (since they are involved in DNA cleavage, stabilisation of protein folding, and drugs) and industrial applications (vulcanising agents, oils, rubber and rechargeable lithium batteries).^{1,3} Therefore, much research efforts have been directed towards the synthesis of disulfides, most approaches involving the oxidation of thiols using oxidants and metal catalysts.⁴ Most disulfide synthetic methodologies are still hampered by the use of hazardous, toxic, or expensive reagents, long reaction times, the formation of over-oxidised undesired products and the need for stoichiometric amounts of reagents.⁴ In this context, the use of catalytic transition metal complexes in the presence of molecular oxygen to prepare disulfides from thiols has also been investigated (Fe/BTC⁵ and Co(π)/phtalocyanine⁶). Aerobic methodologies using heterogeneous catalyst have also been developed.7

Selective homogeneous metal-catalysed thiol coupling without the use of an additional oxidant is also possible (using $[Rh(cod)_2]BF_4^8$ or CpMn(CO)₃/ $h\nu^9$). However, these methodologies possess some drawbacks: in one instance, high catalyst loadings (5 mol%) of an expensive Rh complex are required and the use of laser radiation⁹ to form the active species is needed in the other.

Another important transformation in organosulfur chemistry is the preparation of silyl and boron thioethers. For instance, silylthioethers are widely employed in organic chemistry due to their unique properties and reactivity, being used as a protecting group for carbonyl compounds,¹⁰ in the preparation of unsymmetrical thioethers,¹¹ or even for the synthesis of anomeric thioacetals in oligosaccharide chemistry.¹² Despite these numerous applications, methods for their preparation are quite limited. Thiosilanes are usually obtained through a stoichiometric reaction of chlorosilane and a metal thiolate, such as lithium thiolate.¹³ This procedure requires the prior formation of the metal thiolate, which is a significant shortcoming. In order to develop a more convenient methodology, a catalytic approach has been reported.¹⁴ However, this process requires expensive and highly sensitive reagents such as $B(C_6H_5)_3$.¹⁴ Recently, the silylation of thiols has been described using transition-metal complexes (CpFe(CO)₃Me¹⁵ and Ru₃(CO)₁₂¹⁶), but involve less scalable processes due the use of light-mediated procedures¹⁵ and again relatively high catalyst loadings.^{15,16}

Regarding the formation of S–B bond, boron–sulfur compounds have recently been used as coupling reagents, for example with alkynes¹⁷ and halides.¹⁸ However, there are no reports in the literature of any catalysed methodology for sulfur–boron bond formation.

Recently our group has developed a highly stable $[RuCl(PPh_3)_2-(3-phenylindenyl)]$ complex (1),¹⁹ that has been proven to be highly efficient in a number of reactions such as the racemisation of chiral alcohols,²⁰ the hydrogenation of carbonyl compounds²¹ and the selective oxidation of secondary alcohols.²² Moreover, 1 can be easily and inexpensively synthesised starting from a suitable propargylic alcohol and $[RuCl_2(PPh_3)_3]$ (Scheme 1).²⁰

Taking into account the interest in developing clean, fast and inexpensive methods for S-heteroatom bond formation, we report here the use of **1** as an efficient and versatile catalyst for S–S, S–Si and S–B bond forming reactions, under mild conditions and avoiding the use of any additional oxidant.

$$[RuCl_{2}(PPh_{3})_{3}] + = \bigvee_{Ph}^{OH} \underbrace{AcCl}_{THF} \underbrace{Et_{3}N}_{THF/EtOH} \xrightarrow{Ph}_{Cl} \underbrace{Ru}_{PPh_{3}}^{Fu}$$

Scheme 1 Synthesis of [RuCl(PPh₃)₂(3-phenylindenyl)] (1).

EaStCHEM School of Chemistry, University of St Andrews, St Andrews, KY16 9ST, UK. E-mail: snolan@st-andrews.ac.uk

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 Table 1
 Scope of the thiol oxidation reaction^a

| | 1(CySH — 2a | X mol%) Base DH, 60 °C 1.5 h | 1/2 CySSCy 3a | |
|--------|-----------------------|---------------------------------------|--|-----------|
| Entry | Cat. loading (mol%) | Base | Conversion ^{b,c} (%) | Yield (%) |
| 1 | 5 | KHMDS | >99 | 54 |
| 2 | 5 | KOtBu | >99 | 55 |
| 3 | 5 | K_2CO_3 | >99 | 48 |
| 4 | 5 | Et ₃ N | 77 | 42 |
| 5 | 5 | CsOH | >99 | 70 |
| 6 | 5 | КОН | >99 | 79 |
| 7 | 2.5 | KOH | >99 | 82 |
| 8 | 1 | KOH | 60 | 36 |
| a Deno | tion conditions. CuSL | I (0.25 m | mol) 1 (\mathbf{V} mol 0) | and base |

^{*a*} Reaction conditions: CySH (0.25 mmol), **1** (X mol%) and base (0.25 mmol) in MeOH (0.5 mL). ^{*b*} Determined by ¹H NMR. ^{*c*} Determined by GC using *n*-tetradecane as internal standard.

At first, we investigated the effect of the solvent using the oxidation of cyclohexanethiol (2a) to the corresponding dicyclohexyl disulfide (3a) as a model reaction. Interestingly, MeOH shows an enormous beneficial effect on the reaction, leading to the complete conversion of the thiol (2a) to the corresponding disulfide 3a in only 1.5 h, with a 79% yield (determined by GC, see ESI[†]).

The effect of the base was also evaluated (Table 1). It is possible to perform the reaction in the presence of strong bases such as KHMDS (Table 1, entry 1) and KO^tBu (Table 1, entry 2) or with weaker bases such as K_2CO_3 or NEt₃ (Table 1, entries 3 and 4). However, even though in all cases full conversion was achieved, the reactions show low yields, due to the formation of multiple decomposition products. Hydroxide bases reduced the amount of side products, achieving higher yields (Table 1, entries 5 and 6). The results show that the choice of the counterion (K or Cs) leads to minor yield differences. Potassium hydroxide (KOH)²³ was found to be the best base for the examined system (Table 2, entry 6). In the presence of KOH, the catalyst loading can be decreased to 2.5 mol%, permitting a 82% yield of the dicyclohexyl disulfide (**3a**) (Table 1, entry 7).

After establishing the optimised reaction conditions, the scope of the homocoupling of thiols was examined (Table 2). Several thiols were treated with **1**. Primary and secondary alkyl thiols (Table 2, entries 1 and 2) were converted to the corresponding

| Table 2 | e 2 Scope of the thiol oxidation reaction ^a | | | | |
|--|---|--------------|------------------------|--|--|
| $RSH \begin{array}{c} KOH \\ \hline 1 (2.5 \text{ mol}\%) \\ \hline MeOH, 60 \ ^{\circ}C \\ t \end{array} \begin{array}{c} 1/2 \text{ RSSR} \\ \hline 3 \end{array}$ | | | | | |
| Entry | R-SH (2) | <i>t</i> (h) | Yield ^b (%) | | |
| 1 | Cy-SH (2a) | 1.5 | 82 | | |
| 2 | $C_5H_{11}-SH(2b)$ | 1.5 | 76 | | |
| 3 | tBu-SH(2c) | 3.5 | 50 | | |
| 4 | Bn–SH (2d) | 1.5 | 75 | | |
| 5 | Ph-SH (2e) | 1.5 | 85 | | |
| 6 | $pClC_6H_4$ -SH (2f) | 1 | 55 ^c | | |
| 7 | $pNO_2C_6H_4$ -SH (2g) | 1 | 60^c | | |
| 8 | $pMeOC_6H_4-SH(2h)$ | 2 | 83 | | |

^{*a*} Reactions conditions: RSH (0.25 mmol), **1** (2.5 mol%), KOH (0.25 mmol), dissolved in MeOH (0.5 mL). ^{*b*} Determined by GC using *n*-tetradecane as internal standard. ^{*c*} Isolated yield.

disulfides in good yields (76–82%). It is noteworthy that even hindered tertiary alkyl thiols proved suitable, providing the corresponding disulfide in moderate yield (Table 2, entry 3). Benzyl mercaptan (Table 2, entry 4) was successfully converted in a good yield (75%). To broaden the scope of this reaction, aryl thiols were also tested. Phenyl disulfide was obtained with a very good yield (Table 2, entry 5). Electronic factors play a slight role in the reactivity and the yield (Table 2, entries 5–8). The presence of an electron withdrawing group on the aromatic ring led to shorter reaction times with a slight erosion in yield (Table 2, entries 6–8).

The method was then extended to the coupling between thiols and silanes. At first, a small catalyst loading optimization was performed at 80 °C using toluene as a solvent. This optimisation allowed a significant decrease in the catalyst loading to 0.5 mol% (see ESI[†]). The scope of the sulfur–silicon coupling was next studied using these optimised conditions (Table 3).

Initially, the reaction with triethylsilane (4a) at 80 °C led to the desired compounds with full conversion in the presence of alkyl (primary and secondary) and benzyl thiols (Table 3, entries 2-5). In the case of thiophenol (2e) the reaction required an increase in the temperature up to 110 °C to efficiently yield the desired coupled compound (5e) with full conversion (Table 3, entries 6 and 7). To broaden the reaction scope, several silanes were tested in the presence of cyclohexyl- (2a), benzyl- (2b) and phenylthiol (2c). To achieve higher conversions with these more challenging substrates, the reactions were carried out in refluxing toluene. The system displays very good efficiency and a high compatibility in the S-Si coupling, obtaining full conversions and high turnover numbers (up to 200) regardless of the nature of both thiol and silane (Table 3, entries 8-19), proving to be the best catalyst for this transformation to date.

| Table 3 | Scope of the thiol-silane coupling reaction ^a | | | | |
|----------|--|--|---|--|--|
| | RSH + 2 | R´ ₃ SiH <u>1 (0.5 mo</u> Toluene, 4 16 h | ^{%)} ⊤ª RS−: 5 | SiR′ ₃ | |
| Entry | R-SH (2) | R' ₃ -SiH (4) | T^{a} (°C) | Conversion ^b (%) | |
| 1 | Cy–SH (2a) | Et_3SiH (4a) | 80 | 0^c | |
| 2 3 | $Cy-SH (2a) C_5H_{11}-SH (2b)$ | $Et_3SiH (4a)$ $Et_3SiH (4a)$ | 80 80 | 5a; >99(95) 5b; >99(96) | |
| 4 | C_5H_{10} -SH (2b) | $Et_3SiH(4a)$ | 80 | 5c; >99(94) | |
| 5 6 | Ph-SH $(2\mathbf{c})$ | $Et_3SiH (4a)$ $Et_3SiH (4a)$ | 80 80 | 5 d ; >99(93) 5 e ; 30 | |
| 7 8 | Ph-SH (2e) Cy-SH (2a) | $Et_3SiH(4a)$ PhMe_SiH(4b) | 110 110 | 5e; >99(95) 5f: >99(97) | |
| 9 | Cy-SH (2a) | Ph_2MeSiH (4c) | 110 | 5g; >99(96) | |
| 10 11 | Cy–SH (2a) Cy–SH (2a) | $Ph_3SiH (4d)$ (EtO) ₃ SiH (4e) | $\begin{array}{c} 110 \\ 110 \end{array}$ | 5h; >99 5i; >99(99) | |
| 12 | Bn–SH (2d) | $PhMe_2SiH$ (4b) | 110 | 5j; >99(92) | |
| 13 14 | Bn–SH (2 d) Bn–SH (2 d) | $Ph_2MeSiH (4c)$ $Ph_3SiH (4d)$ | $\frac{110}{110}$ | 5k; >99(97) 5l; >99 | |
| 15 | Bn-SH $(2d)$ | $(EtO)_3SiH$ (4e) | 110 | 5 m ; >99(99) | |
| 16 17 | Ph-SH(2e) Ph-SH(2e) | $PhMe_2SiH (4b)$ $Ph_2MeSiH (4c)$ | 110 110 | 5 n; >99(95) 5 o; >99(97) | |
| 18 19 | Ph-SH (2e) Ph-SH (2e) | $Ph_{3}SiH (4d)$ (EtO) ₃ SiH (4e) | 110 110 | 5p; >99 5q; >99(99) | |

^{*a*} Reaction conditions: RSH (0.25 mmol), R'_3 SiH, (0.55 mmol), 1 (2.5 mol%) in toluene (0.5 mL). ^{*b*} Determined by ¹H NMR. Isolated yield in brackets. ^{*c*} In the absence of catalyst (1).

Table 4 Coupling between thiols and boron reagents^a

| | RSH + H-B 0 2 6 | → 1 (0.5 mol%) Toluene, 60 °C 16 h | $RS-B_{0}^{O}$ |
|-------|-----------------------|--|-------------------------------------|
| Entry | Borane (6) | R-SH (2) | Conversion ^b (%) |
| 1 | pinBH | Cy–SH (2a) | 0 ^c |
| 2 | pinBH | Cy-SH (2a) | 7a ; >99 |
| 3 | pinBH | $C_{5}H_{11} - SH(2b)$ | 7 b ; >99 |
| 4 | pinBH | Bn-SH (2d) | 7c; >99 |
| 5 | pinBH | Ph-SH (2e) | 7 d ; >99 |
| 6 | catBH | Cy–SH (2a) | 7e ; >76 ^{<i>d</i>} |
| 7 | catBH | Bn-SH (2d) | $7f; >70^d$ |
| 8 | catBH | Ph-SH (2e) | 7g ; >89 ^{<i>d</i>} |

^{*a*} Reaction conditions: RSH (0.25 mmol), borane (0.55 mmol) and **1** (2.5 mol%) dissolved in toluene (0.5 mL). ^{*b*} Determined by ¹H NMR spectroscopy. ^{*c*} In the absence of catalyst (**1**). ^{*d*} Desired coupled products (7e-7g) could not be isolated as pure compounds.

To further extend the generality and the activity of **1**, boroncontaining substrates were subjected to the silicon coupling optimised conditions (Table 4). Initially, the reaction in the presence of pinacolborane (**6a**) was studied. It is noteworthy that, again, the efficiency of the transformation is not dependent on the nature of the thiol. Thus, reactions in the presence of alkyl, benzyl and aryl thiols take place with full conversion and with a high turnover number (TON: 200) (Table 4, entries 2–5). Catecholborane (**6b**) successfully afforded the expected product in the presence of thiophenol (**2e**) (Table 4, entry 8). However, the cyclohexyl- (**2a**) and the benzylthiol (**2d**) did not lead to the desired coupled compound with the same efficiency (Table 4, entry 8).

In summary, we have established a very general and simple methodology for coupling reactions between thiols and other heteroatom-containing substrates catalysed by $[RuCl(PPh_3)_2-(3-phenylindenyl)]$ (1). Disulfides can be obtained in good yields under mild conditions. 1 shows the best activity to date (turnover number up to 200) in the dehydrogenative coupling between thiols and silanes to give the corresponding silylthioethers. We have also demonstrated the utility of 1 in the first-reported catalysed coupling reaction between thiols and boranes, representing a very efficient (turnover number up to 200) and simple approach to the preparation of alkyl and aryl thiodioxaborolanes. Further studies are ongoing in our laboratory to evaluate the catalytic potential of 1 in related reactions.

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