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Highly regio- and stereoselective hydrothiolation of acetylenes with thiols catalyzed by a well-defined supported Rh complex†

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Highly regio- and stereoselective hydrothiolation of a wide range of alkynes with various thiols was demonstrated in the presence of a well-defined Rh complex supported on mesoporous SBA-15 silica. The catalyst was easily recovered and reused several times without significant loss of activity or selectivity.

Transition metal catalyzed addition of an S–H bond to alkynes is a straightforward and atom-efficient method for the formation of stereo- and regio-defined vinyl sulfides, which are versatile intermediates for synthesis of biologically active compounds, organic building blocks, and new materials.[1] Several metal-based homogeneous catalysts such as Rh,[2] Ir,[3] Ni,[4] Pd,[5] Pt,[6] Au,[7] Zr,[8a] and f-elements[8b–d] have been developed to produce regio- and stereoselective vinyl sulfides. Among these transition metal complexes investigated, rhodium complexes have received considerable attention, due to their high activity and regio- and stereoselectivity for either Markovnikov or anti-Markovnikov products under mild reaction conditions.[2] However, industrial applications of these homogeneous rhodium complexes remain a challenge because they are expensive, cannot be recycled, and difficult to separate from the product mixture, which is a particularly significant drawback for their application in the pharmaceutical industry. The immobilization of catalytically active species, *i.e.* organometallic complexes, onto a solid support to produce a molecular heterogeneous catalyst is one potential solution to the latter two problems.[9] The merits of surface organometallic catalysts are derived not only from their ease of separation from the reaction media but also their unique activity derived from their site-isolation and the structure of their active sites.

The immobilization of rhodium complexes through covalent bond formation with functional groups on silica is the most commonly employed method to form surface organometallic catalysts that are applicable for a variety of catalytic chemistries including hydrogenation,[10] hydroformylation,[11] and hydrosilylation.[12] These structures reduce rhodium leaching from the support and subsequent metal contamination of the products, and can even provide an enhancement in the reactivity, selectivity and/or enantioselectivity in some cases.[10,11] The chemical bonding between metal complexes and functional groups of the support maintains the isolated nature of metal complexes, which can influence the catalytic performance in a manner that the analogous homogeneous complex does not exhibit in solution.[13] In spite of tremendous effort dedicated to the immobilization of homogeneous complexes over the last two decades, very few examples of alkyne hydrothiolation with thiols catalyzed by heterogeneous catalysts with high activity and excellent regio- and stereoselectivity have appeared.[6] Therefore, the development of a stable heterogeneous rhodium catalyst that allows for highly regio- and stereoselective hydrothiolation of a wide range of substrates (thiols and alkynes) is worthwhile. Herein, we report the highly regio- and stereoselective hydrothiolation of alkynes with thiols catalyzed by a well-defined heterogeneous rhodium complex catalyst supported on SBA-15 under mild reaction conditions.

Preparation of the supported rhodium complexes on SBA-15, labeled as Rh–P–SBA-15, Rh–N–SBA-15, and Rh–2N–SBA-15, respectively, was performed under a nitrogen atmosphere in a step-by-step manner (Scheme S1, ESI†). Characterization results from BET, XRD, and HR-TEM (Table S1, Fig. S1–S3, ESI†) for a Rh–P–SBA-15 catalyst show that the ordered mesoporous channel structure was preserved upon functionalization and immobilization of $RhCl(PPh_3)_3$ occurred within the pores. The appearance of new peaks at δ = 18, 26, 33, 58, 68, and 128–132 ppm in the ^{13}C solid-state NMR spectrum further reveals that the biphenylphosphine–propyl linker was grafted onto the SBA-15 surface (Fig. 1). The ^{31}P solid-state NMR spectrum (Fig. S5, ESI†) exhibited a broad resonance centered at δ = 28.0 ppm corresponding to the Rh–P complex along with a strong peak at δ = −15.8 ppm assignable to the free biphenylphosphine ligand of the linker, indicating that both the biphenylphosphine ligand and $RhCl(PPh_3)_3$ were successfully grafted and immobilized onto SBA-15, respectively. There was no indication of an oxidized phosphine peak at δ = 38.0 ppm, or phosphonium species at δ = 24.0 ppm.[14] The loading of the immobilized rhodium complex was 0.92 wt% (Rh), which corresponds to a rhodium density of 0.09 nm^{-2}. This density ensured that the probability of individual rhodium complexes that are site-isolated was high.

Our initial efforts concentrated on the optimization of the reaction conditions for the regio-defined synthesis of vinyl sulfides. The addition of phenylacetylene (**2a**) to thiophenol (**1a**) was chosen as a model reaction, and the results are compiled in

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† Electronic supplementary information (ESI) available: General information, experimental details, catalyst characterization and recyclability data and $^1H/^{13}C$ NMR, HR-MS data for (*E*)-vinyl sulfides. See DOI: 10.1039/c1cc11605c

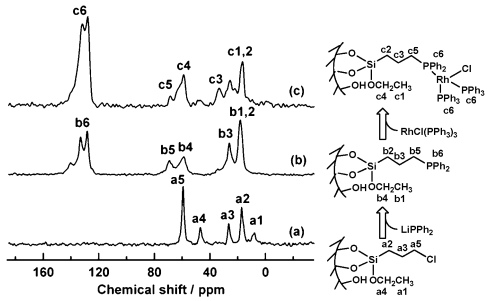
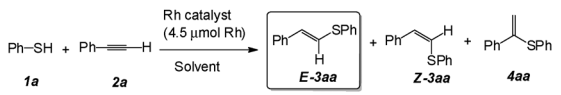


Fig. 1 ^{13}C solid-state NMR spectra of (a) Cl–SBA-15; (b) P–SBA-15; and (c) Rh–P–SBA-15.

Table 1. Wilkinson's catalyst, $RhCl(PPh_3)_3$, exhibited high activity and excellent regio- and stereoselectivity, achieving up to 98% conversion and 94% selectivity to *E*-**3aa** in DCE (1,2-dichloroethane) solution within 45 min at room temperature (Table 1, entry 1). Upon immobilization of $RhCl(PPh_3)_3$ onto the functionalized SBA-15, the regio- and stereoselectivity depended on the functional groups linked to the rhodium complex. Markovnikov addition was totally suppressed. The stereoselectivity could be switched by the type of functional group linked to SBA-15. The addition of **2a** to **1a** catalyzed by Rh–N–SBA-15 gave a mixture of anti-Markovnikov ((*E* + *Z*)-**3aa**) products with the (*Z*)-isomer (**3aa**) as the main product (Table 1, entry 2). The catalyst Rh–2N–SBA-15 produced excellent regio- and stereoselectivity to *Z*-**3aa** with activity comparable to Rh–N–SBA-15 (Table 1, entry 3). In sharp contrast, exclusive and reversed regio- and stereoselectivity to *E*-**3aa** with a slightly higher conversion was obtained for this transformation in the presence of Rh–P–SBA-15 under otherwise identical reaction conditions (Table 1, entry 4). In order to synthesize (*E*)-anti-Markovnikov vinyl sulfides with Rh–P–SBA-15, we next investigated the influence of solvents on this transformation. With solvents such as ethanol, toluene, ethyl acetate (EtOAc), and hexane, only *E*-**3aa** was obtained but with reduced activity compared to DCE (Table 1, entries 5–8). The Markovnikov addition product **4aa** was produced simultaneously when the reaction was performed with some solvents, such as dichloromethane, acetone, and THF (Table 1, entries 9–11). Among the solvents investigated, DCE was found to be the best choice for the formation of the (*E*)-anti-Markovnikov vinyl sulfide product. In addition, the transformation catalyzed by Rh–P–SBA-15 proceeded to >80% conversion in the presence of galvinoxy, a free radical inhibitor (galvinoxy/Rh = 3, molar ratio), ruling out the possibility that a radical mechanism contributes to the formation of the anti-Markovnikov addition product (Table 1, entry 12).

Table 1 Hydrothiolation of thiophenol with phenylacetylene under different conditions[a]

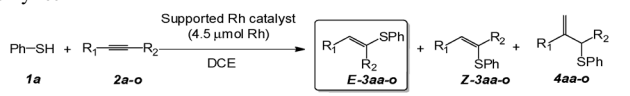


Entry	Catalyst	Solvent	Conv[b]/%	Selectivity[c]/% (*Z* + *E*):**4aa**	*E*:*Z*
1[d]	$RhCl(PPh_3)_3$	DCE	98	94:6	100:0
2	Rh–N–SBA-15	DCE	84.3	>99:1	29:71
3	Rh–2N–SBA-15	DCE	74.9	>99:1	1:99
4	Rh–P–SBA-15	DCE	87.5	>99:1	100:0
5	Rh–P–SBA-15	EtOH	34.4	>99:1	100:0
6	Rh–P–SBA-15	Toluene	74.2	>99:1	100:0
7	Rh–P–SBA-15	EtOAc	7.4	>99:1	100:0
8	Rh–P–SBA-15	Hexane	62.0	>99:1	100:0
9	Rh–P–SBA-15	CH_2Cl_2	96.4	65:35	100:0
10	Rh–P–SBA-15	Acetone	96.9	94:6	100:0
11	Rh–P–SBA-15	THF	14.6	96:4	100:0
12[e]	Rh–P–SBA-15	DCE	81.8	93:7	100:0

[a] Reaction conditions: 0.5 mmol phenylacetylene, 0.55 mmol thiophenol, 50 mg catalyst (4.5 μmol Rh), 2 mL solvent, room temperature and a reaction time of 20 h. [b] Conversion of phenylacetylene. [c] Determined by ^1H NMR analysis of the crude mixture. [d] Reaction time of 45 min. [e] In the presence of 3 mol% galvinoxyl free radical inhibitor.

Encouraged by this discovery, the scope of alkynes was next studied using **1a** as the thiol substrate in the presence of Rh–P–SBA-15 in DCE; the results are summarized in Table 2. Aromatic, aliphatic, and internal alkynes were hydrothiolated to the (*E*)-anti-Markovnikov products with moderate to high conversion with excellent regio- and stereoselectivity. Electron-rich and electron-poor substituents at the 3 and 4 positions on the phenyl ring of aromatic alkynes all gave satisfactory conversions (Table 2, entries 2, 4, 5, 7, and 8). A methyl group at the 2-position (**2ac**) did not hinder the reaction, but a methoxy group at the same position (**2af**) significantly decreased the conversion (Table 2, entries 3 and 6). Aliphatic alkynes reacted with **1a** to afford the corresponding (*E*)-anti-Markovnikov vinyl sulfides with satisfactory conversion and exclusive regio- and stereoselectivity, but required either a considerably longer reaction time, elevated temperature or both (Table 2, entries 9–13). The internal alkyne 1-phenyl-1-propyne (**2an**) underwent stereoselective hydrothiolation but also required a longer reaction time (Table 2, entry 14); however no addition products were isolated when the transformation of diphenylacetylene (**2ao**) with **1a** was performed under otherwise identical reaction conditions (Table 2, entry 15).

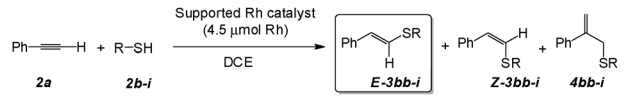
Table 2 Catalytic hydrothiolation of thiophenol with a wide range of alkynes[a]



Entry	R_1	R_2	Temp/°C	Conv[b]/%	Selectivity[c]/% (*E* + *Z*):**4aa-o**	*E*:*Z*
1[d]	Ph	H **2aa**	25	87.5	>99:1	100:0
2[d]	4-Me–Ph	H **2ab**	25	83.6	>99:1	100:0
3[d]	2-Me–Ph	H **2ac**	25	78.6	>99:1	100:0
4[d]	3-Me–Ph	H **2ad**	25	85.9	>99:1	100:0
5[d]	4-MeO–Ph	H **2ae**	25	83.8	>99:1	100:0
6[d]	2-MeO–Ph	H **2af**	25	62.2	>99:1	100:0
7[d]	4-F–Ph	H **2ag**	25	81.8	98:2	100:0
8[d]	4-Br–Ph	H **2ah**	25	80.2	98:2	100:0
9[e]	n-C_5H_{11}	H **2ai**	60	72.3	>99:1	100:0
10[e]	n-$C_{10}H_{21}$	H **2aj**	60	76.6	>99:1	100:0
11[e]	HO–(C_2H_4)	H **2ak**	60	97.6	>99:1	100:0
12[e]	Cl–(C_2H_4)	H **2al**	60	98.0	>99:1	100:0
13[e]	Cyclohexene	H **2am**	25	86.0	>99:1	100:0
14[e]	Ph	Me **2an**	60	68.4	>99:1	100:0
15[e]	Ph	Ph **2ao**	60	n.r[f]	n.r	n.r

[a] Reaction conditions: 0.5 mmol alkynes, 0.55 mmol thiophenol, 50 mg catalyst (4.5 μmol Rh) and 2 mL DCE. [b] Conversion of alkynes. [c] Determined by ^1H NMR analysis of the crude mixture. [d,e] Reaction time of 20, 40 h. [f] No reaction.

Table 3 Catalytic hydrothiolation of phenylacetylene with a wide range of thiols[a]



Entry	R	Temp/°C	Time/h	Conv[b]/%	Selectivity[c]/% (*E* + *Z*): **4bb-i**	*E*:*Z*
16	4-Me–Ph **2bb**	25	20	87.5	>99 : 1	100 : 0
17	4-MeO–Ph **2bc**	25	20	83.6	>99 : 1	100 : 0
18	4-Cl–Ph **2bd**	25	20	78.6	>99 : 1	100 : 0
19	4-Br–Ph **2be**	25	20	85.9	>99 : 1	100 : 0
20	$PhCH_2$ **2bf**	60	40	83.8	91 : 9	100 : 0
21	Cyclohexane **2bj**	60	40	62.2	80 : 20	100 : 0
22	CH_3CH_2 **2bh**	60	40	81.8	71 : 29	100 : 0
23	CF_3CH_2 **2bi**	60	24	80.2	92 : 8	100 : 0

[a] Reaction conditions are the same as Table 2. [b] Conversion of alkynes. [c] Determined by ^{1}H NMR analysis of the crude mixture.

Functional groups such as fluoro, chloro, hydroxyl, methoxy, and olefinic were compatible with this catalytic system (Table 2, entries 7, 8, and 11–13). In all cases listed in Table 2, the corresponding disulfide adduct was not formed as a byproduct and no double bond dimerization occurred.

Likewise, various aromatic and aliphatic thiols reacted with **2a** in the presence of Rh–P–SBA-15 with high conversion with good to excellent regio- and stereoselectivity in DCE, as shown in Table 3. Phenylacetylene (**2a**) reacted efficiently with aromatic thiols bearing electron-rich or electron-poor groups on the phenyl ring with excellent regio- and stereoselectivity (Table 3, entries 16–19). The addition of aliphatic thiols to **2a** proceeded smoothly and required both longer reaction time and higher temperature to achieve satisfactory conversion (Table 3, entries 20–23). Notably, unlike aromatic thiols, the regioselectivity of aliphatic thiols transformation highly depended on the substrates involved. For instance, the regioselectivity to **3bf** and **3bi** was 91 and 92% (Table 3, entries 20 and 23), but only 80 and 71% for **3bj** and **3bh** and 20 and 29% for **4bj** and **4bh** were obtained, respectively (Table 3, entries 21 and 22).

To verify whether the observed catalysis was due to the heterogeneous catalyst Rh–P–SBA-15 or a leached rhodium species in solution, we carried out the addition of phenylacetylene (**2a**) to thiophenol (**1a**) and removed the catalyst from the reaction mixture by filtration at approximately 50% conversion of **2a** (Fig. S6, ESI†). After removal of the Rh–P–SBA-15 catalyst, the filtrate was again held at room temperature under an atmosphere of N_2. In this case, no significant increase in conversion was observed, indicating that leached Rh species from the catalyst (if any) are not responsible for the observed activity. It was confirmed by ICP-AES analysis that no rhodium species could be detected in the filtrate (below the detection limit). The Rh–P–SBA-15 catalyst could be recovered by filtration and reused at least 6 times for the transformation of **1a** and **2a** without any significant loss of catalytic activity and regioselectivity, as shown in Fig. S7 (ESI†). Together, these results rule out any contribution to the observed catalysis from a homogeneous rhodium species demonstrating that the observed catalysis was intrinsically heterogeneous. It is worthy to note that both the catalytic activity and regioselectivity decreased slightly after the fourth run, possibly due to the oxidation of the phosphine ligands by traces of air entering the system during the refilling steps.

In summary, a well-defined supported rhodium catalyst has been developed for the hydrothiolation of alkynes with thiols. Due to the high activity and excellent regio- and stereoselectivity of the heterogeneous catalyst, the process represents a green methodology for synthesizing regio-defined vinyl sulfides and extends the synthetic utility of hydrothiolation reactions. Further studies are underway on the scope of other substrates and in understanding the role of the functional groups grafted to the silica surface in the reaction regio- and stereoselectivity.

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