Highly efficient catalytic dehydrative S-allylation of thiols and thioic *S*-acids†

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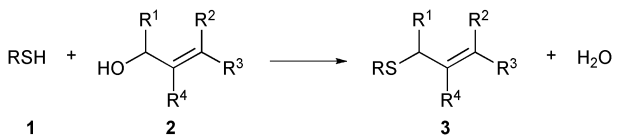
A SH-selective allylation method using [CpRu(2-quinolinecarboxylato)(η_3-C_3H_5)]PF_6 has been realized in various solvents including aqueous media to give allyl sulfides and allyl *S*-thioates, demonstrating the potential applicability to lipopeptide chemistry.

Allyl sulfides and their α-oxo derivatives, *S*-allyl thioates, play an important role in bioorganic chemistry[1] and serve as useful synthetic elements for organic synthesis.[2] The allylic C=C double bond, allylic proton, and sulfur group expand the type of reactions that can be achieved, facilitating useful transformations of organic molecules. The preparation is based mainly on base-/acid-promoted[3] or transition-metal-catalyzed[4,5] coupling between thiols and activated allyl electrophiles among many other methods. Catalytic dehydrative allylation of thiols and thioic *S*-acids **1** with allyl alcohols **2** to give **3** is apparently the most straightforward and ideal in terms of atom economy, E factor, safety and operational simplicity.[6] Several such trials have been reported in the literature.[5,7–9] Among these examples, Cp*Ru(II)Cl(cod) by Kondo *et al.*[5] and Pd(0)($P(C_6H_4(SO_3Na))_3)_3$ by Komiya *et al.*[8] are the most promising catalyst systems. Indeed, the Ru chemistry has been significantly improved by Pregosin to give an excellent [Cp*Ru(II)$(CH_3CN)_3$]PF_6/TsOH combined system.[9a] We have independently developed a new catalytic system enabling the activation of an allyloxy C–O bond on the basis of a "redox-involved donor–acceptor bifunctional catalyst (RDACat) concept."[10] The system, consisting of [CpRu(II)$(CH_3CN)_3$]PF_6 (**4**) and 2-quinolinecarboxylic acid (QAH) or the π-allyl complex [CpRu(IV)(η^3-C_3H_5)QA]PF_6 (**5**), efficiently catalyzes the dehydrative allylation of alcohols with high versatility to give allyl ethers.[11] We reasoned that utilizing these complexes would facilitate the necessary juxtaposition of S-allylation with O-allylation.



Catalytic performance was initially investigated using a fixed set of conditions ([$C_6H_5CH_2SH$] = 1000 mM, [CH_2=$CHCH_2OH$] = 1000 mM, [Cp or Cp*Ru catalyst] = 1.0 mM, CH_2Cl_2, 30 °C). The results are shown in Table 1. The CpRu complex **4** itself slowly catalyzed the reaction to give **3** (R^1 = R^2 = R^3 = R^4 = H) in 17% yield after 1 h, but the reaction nearly stopped at *ca.* 20% conversion (entry 1). A combination of **4** with QAH considerably increased catalysis (84%, 1 h), and the reaction was almost completed in 3 h (entry 2). The π-allyl complex **5** gave a similar level of reactivity to **4**/QAH-combined system (*vide infra*). Introduction of a methyl group at C(8) of QAH abolished the acceleration effect (entry 3). A similar result was observed with 2-pyridinecarboxylic acid (PAH) and 6-*t*-C_4H_9–PAH (55% *vs.* 16%, 3 h) (entries 4 and 5). [Cp*Ru(II)$(CH_3CN)_3$]PF_6 (**6**) itself displayed little reactivity (entry 1). PAH promoted the allylation more efficiently than QAH (72% *vs.* 97%, 12 h), unlike CpRu (entries 2 and 4). No reaction occurred with both 8-CH_3–QAH and 6-*t*-C_4H_9–PAH (entries 3 and 5). A combination of either **4** or **6** with simple Brønsted acids such as C_6H_5COOH, 4-$CH_3C_6H_4SO_3H$, CF_3SO_3H, and HCl also showed less reactivity (entries 6–9).[12] A series of experiments indicate that the coordination of sp^2N atom to the central Ru metal plays a key role in achieving high levels of reactivity and robustness. Complex formation is retarded by increased steric repulsion between the ligands on Ru, resulting in Cp*Ru/PAH > Cp*Ru/QAH. The lower LUMO level of QAH in comparison to PAH would explain CpRu/QAH > CpRu/PAH.[11c]

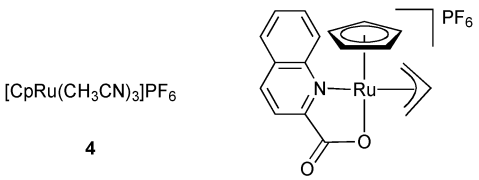


Table 2 shows the solvent effect and the applicability to other allyl alcohols by use of phenylmethanethiol and **5** (for further details see ESI†). CH_2Cl_2, DMF, DMA, THF, and CH_3OH (entries 1, 4, 5, 7 and 9) were the solvents of choice. The same results were obtained using C_2H_5OH, *i*-C_3H_7OH, and *t*-C_4H_9OH, but the rate of reaction was slower in CH_3CN or toluene (entries 6 and 8). Even in water-containing CH_3OH, dehydrative allyl sulfide formation proceeded quantitatively (entry 10). No solvent afforded **3** (R^1 = R^2 = R^3 = R^4 = H) in 98% isolated yield (10 mmol scale). Introduction of one methyl group at the C(1), C(2), or C(3) position of $C(3)H_2$=$C(2)HC(1)H_2OH$ exerted little effect on the reactivity in CH_3OH (entries 11–13). The CH_3 substituent at C(2) could be replaced with *n*-C_6H_{13}, C_6H_5 and $COOC_2H_5$ groups without any deceleration (entries 14, 16 and 17). However, secondary alkyl substitution did decrease the rate

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† Electronic supplementary information (ESI) available: General procedures for the allylation and characterization of all of the allylation products. See DOI: 10.1039/c0cc00096e

Table 1 Acid effect on the reactivity in the reaction of phenylmethanethiol with allyl alcohol in the presence of $[CpRu(CH_3CN)_3]PF_6$ or $[Cp^*Ru(CH_3CN)_3]PF_6$[a]

		Convn (%) using $[CpRu(CH_3CN)_3]PF_6$[b]				Convn (%) using $[Cp^*Ru(CH_3CN)_3]PF_6$[b]			
Entry	Additive	1 h	3 h	12 h	24 h	1 h	3 h	12 h	24 h
1	—	17	20	24	24	<1	<1	1	1
2	QAH[c,d]	84	95	98	>99	15	45	72	81
3	8-CH_3–QAH[d,e]	15	18	24	25	0	<1	<1	<1
4	PAH[d,f]	39	55	69	70	26	69	97	>99
5	6-*t*-C_4H_9–PAH[d,g]	11	16	23	34	0	<1	<1	<1
6	C_6H_5COOH	14	18	25	26	<1	<1	2	5
7	4-$CH_3C_6H_4SO_3H$	12	22	53	59	0	<1	2	4
8	CF_3SO_3H	19	22	33	34	<1	<1	2	4
9	HCl	6	8	14	20	1	2	6	11

[a] All reactions were carried out by successive addition of a solution of a Ru precursor, allyl alcohol, and then phenylmethanethiol under the following conditions unless otherwise specified: 3 mmol of thiol in CH_2Cl_2; $[C_6H_5CH_2SH]$ = [**2** (CH_2=$CHCH_2OH$)] = 1000 mM; [$[CpRu(CH_3CN)_3]PF_6$ or $[Cp^*Ru(CH_3CN)_3]PF_6$] = 1 mM; temp., 30 °C. [b] ^{1}H-NMR analysis of the crude products obtained after $(C_2H_5)_3N$ addition for quenching. The conversions are nearly identical with the yields of allyl phenylmethyl sulfide. [c] 2-Quinolinecarboxylic acid. [d] H in QAH and PAH represents the carboxylic acid proton. [e] 8-Methyl-2-quinolinecarboxylic acid. [f] 2-Pyridinecarboxylic acid. [g] 6-*tert*-Butyl-2-pyridinecarboxylic acid.

Table 2 Solvents and allyl alcohols usable in the catalytic dehydrative allylation of phenylmethanethiol in the presence of $[CpRu(\eta^3\text{-}C_3H_5)(QA)]PF_6$ (**5**)[a]

	2					
Entry	R^1	R^2	R^3	R^4	Solvent	Yield[b] (%)
1	H	H	H	H	CH_2Cl_2	98
2	H	H	H	H	CH_2Cl_2	97[c,d]
3	H	H	H	H	CH_2Cl_2	95[e]
4	H	H	H	H	DMF	97
5	H	H	H	H	DMA	97
6	H	H	H	H	CH_3CN	60
7	H	H	H	H	THF	98
8	H	H	H	H	Toluene	90
9	H	H	H	H	CH_3OH	99[c]
10	H	H	H	H	1 : 1 CH_3OH–H_2O	98
11	CH_3	H	H	H	CH_3OH	98[f,g]
12	H	H	CH_3	H	CH_3OH	98[f,h]
13	H	H	H	CH_3	CH_3OH	98
14	H	H	H	*n*-C_6H_{13}	CH_3OH	98
15	H	H	H	*c*-C_6H_{11}	CH_3OH	91
16	H	H	H	C_6H_5	CH_3OH	97
17	H	H	H	$COOC_2H_5$	CH_3OH	96

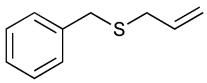
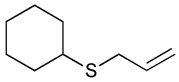
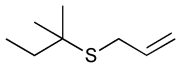
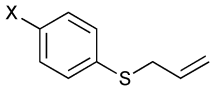
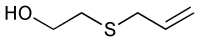
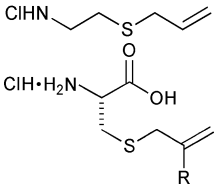
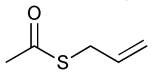
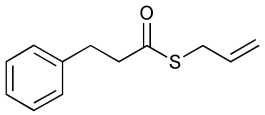
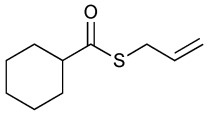
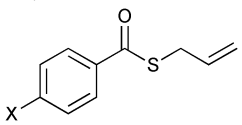
[a] All reactions were carried out under the following conditions unless otherwise specified: 0.4–1 mmol of phenylmethanethiol; [**1**] = [**2**] = 100 mM; [**5**] = 1 mM; temp., 30 °C; 3–4 h. [b] Isolated yield. [c] 3 mmol scale. [**1**] = [**2**] = 1000 mM; [**4**] = 1 mM; 24 h. [d] 84% convn after 1 h. [e] 3 mmol scale. [**1**] = 1000 mM; [**2**] = 2000 mM; [**4**] = 0.2 mM; 48 h. [f] A mixture of benzyl but-3-en-2-yl sulfide, (*E*)- and (*Z*)-benzyl but-2-enyl sulfide. [g] 1 : 0.19 : 0.01 ratio. [h] 1 : 0.39 : 0.09 ratio.

(entry 15). Moreover, no product was obtained at all in the presence of a tertiary alkyl group at C(2). With cyclohex-2-en-1-ol, the reaction was sluggish. A C(3)-dimethyl substituted allyl alcohol, 3-methylbut-2-en-1-ol, showed little reactivity, while the C(1)-dimethyl substituted molecule, 2-methylbut-3-en-2-ol, gave a 1.7 : 1 branch/normal mixture of benzyl 2-methylbut-3-en-2-yl sulfide and benzyl 3-methylbut-2-enyl sulfide in 97% isolated yield.

A variety of thiols can be utilized in the present catalytic system as shown in Table 3 (for further details see ESI†). Primary, secondary, and even tertiary alkyl thiols were allylated (entries 1–3) unlike the case with the corresponding alcohols.[11a] Reaction of aryl thiols with allyl alcohol also proceeded smoothly (entries 4–6). Bifunctional 2-thioethanol and 2-thioethylamine hydrochloride predominantly gave S-allylated products (entries 7 and 8). Even with more acidic thioic *S*-acids than aryl thiols, the *S*-allyl thioates were obtained in >95% yields (entries 11–15). The present dehydrative S-allylation of thiols and thioic *S*-acids can function in an aqueous system, which is a substantial advantage for the allylation of highly polar substrates such as amino acids and peptides. The utility of this reaction was successfully demonstrated by use of cysteine hydrochloride (**7**). A 1 : 1 mixture of **7** and allyl alcohol in an aqueous solvent containing **5** gave *S*-allyl cysteine (**8a**) in >95% yield (S/C = 100, 1 h; S/C = 1000, 24 h) (entry 9). With 2-*n*-C_6H_{13}-substituted allyl alcohol **8b** was obtained in 99% yield (entry 10). The results indicate the potential applicability to lipopeptide chemistry.[1,3c,f–h]

In summary, we have developed an efficient synthetic method for allyl sulfides and α-oxo derivatives using allyl alcohols without any need for activation. Water is the only co-product. The generic reaction proceeds with a high level of chemoselectivity in various aprotic and protic solvents, including water. As well as sterically demanding thiols, electron deficient thiols and thioic *S*-acids can also be utilized as substrates. The detailed mechanism of this reaction is unclear. Nevertheless, the evident high performance of the reaction, even when using a large molar amount of highly-coordinative sulfur-containing compound, can be ascribed to the following characteristics: (i) the chelation ability of QAH that avoids pathways leading to a dead catalyst, (ii) a rapid and exothermic transformation from $[CpRu(II)(QAH)]^+$/allyl alcohol to $[CpRu(IV)(\eta^3\text{-}C_3H_5)(QA)]^+/H_2O$ on the basis of the RDACat mechanism,[10,11] (iii) the high oxophilicity of the carboxylic acid proton of ligating QAH towards the allylic oxygen atom, (iv) no inhibition of products that are associated with the Ru(IV) complex in the resting state, and (v)

Table 3 $[CpRu(\eta^3\text{-}C_3H_5)(QA)]PF_6$ (**5**)-catalyzed allylation of thiols and thioic *S*-acids[a]

Entry	Product **3**	Yield[b] (%)
1		96[c,d] (97)[c,d]
2		97 (97)
3		95 (98)
		
4	X = H	99 (99)
5	X = CH_3O	98 (98)
6	X = Cl	95 (94)
7		97 (96)
8		98 (—)
9	**8a**: R = H	>95[e] (—)
10	**8b**: R = *n*-C_6H_{13}	99[e] (—)
11		— (96)[c,d]
12		98 (97)
13		96 (98)
		
14	X = H	99 (96)
15	X = CH_3O	96 (96)

[a] All reactions were carried out under the following conditions unless otherwise specified: CH_3OH and/or CH_2Cl_2; [**1**] = [**2**] = 100 mM; [**5**] = 1 mM; 25–30 °C; 3–4 h. [b] Isolated yields. Values in the parentheses are those obtained in CH_2Cl_2. [c] 100 mmol scale. [d] [**1**] = [**2**] = 1000 mM; [**5**] = 1 mM; 30 °C; 24 h. [e] 1 : 1 H_2O–CH_3OH was used as the solvent.

near-irreversibility of allyl sulfide formation, unlike allyl ether formation. Studies aimed at determining the mechanism of the reaction as well as its application to asymmetric synthesis are currently underway in our laboratory.

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Notes and references

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12 The $[Cp^*Ru(CH_3CN)_3]PF_6$/4-$CH_3C_6H_4SO_3H$ is reported to show a high reactivity (phenylmethanethiol (0.07 mmol), allyl alcohol (0.07 mmol), catalyst (0.0035 mmol), CD_3CN (0.5 mL): 11 min, quant). See, ref. 9.

