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Communication

Addition of S–H Bonds across Electron-Deficient Olefins Catalyzed by Well-Defined Copper(I) Thiolate Complexes

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A series of monomeric (NHC)Cu(SR) (R = Ph or CH_2Ph; NHC = *N*-heterocyclic carbene) complexes have been synthesized and fully characterized including single-crystal X-ray diffraction studies. These complexes catalyze the addition of S–H bonds across electron-deficient olefins to regioselectively produce “anti-Markovnikov” products.

C–S bonds are prevalent in many important pharmaceutical products such as 6-mercaptopurine (leukemia), tagamet (antiulcer), and thorazine (antipsychotic) as well as other compounds of biological interest or industrial relevance.[1] Recent efforts directed toward the development of routes for C–S bond formation include the addition of S–H bonds across alkynes,[2] episulfide formation,[3] transition-metal-catalyzed sulfur substitution of halides, and thiocarbonylation.[4] The direct addition of S–H bonds across olefins provides an atom economical pathway for C–S bond formation. Additions of S–H bonds to activated olefins under acidic or basic conditions are known;[5–13] however, some limitations exist for these technologies.[14] Although sulfur poisoning is a potential obstacle to catalyst development[15] and reports are limited relative to catalysis under acidic or basic conditions, some examples of transition-metal-catalyzed addition of S–H bonds to electron-deficient olefins have been reported.[12,16–18]

Our group has been interested in the preparation of isolable monomeric copper(I) complexes with anionic heteroatomic ligands (e.g., amido, alkoxo, etc.).[19–21] We have recently reported that copper(I) amido, alkoxo, and related systems serve as catalysts for the “anti-Markovnikov” addition of amines and alcohols to electron-deficient olefins.[22] Herein, we report on the synthesis and characterization of (NHC)Cu(SR) (NHC = *N*-heterocyclic carbene; R = Ph or CH_2Ph) complexes and their use as catalysts for the regioselective hydrothiolation of electron-deficient olefins (Scheme 1).

For this study, the three NHC ligands IPr, IMes, and SIPr [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene; SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene] were utilized (Chart 1).[23–27] The previously reported copper(I) methyl complexes (NHC)Cu(Me)[21,28] react with benzenethiol or benzylmercaptan to cleanly form (NHC)Cu(SR) systems with

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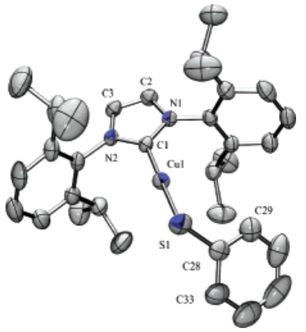


Figure 1. ORTEP of (IPr)Cu(SPh) (**1**) (30% probability; H atoms omitted). Selected bond distances (Å): Cu1−C1 1.895(2), Cu1−S1 2.139(1), S1−C28 1.779(2). Selected bond angles (deg): C1−Cu1−S1 178.3(1), C28−S1−Cu1 100.5(1), N2−C1−Cu1 130.0(1), N1−C1−Cu1 125.5(1).

Scheme 1. Synthesis of (NHC)Cu(SR) Complexes

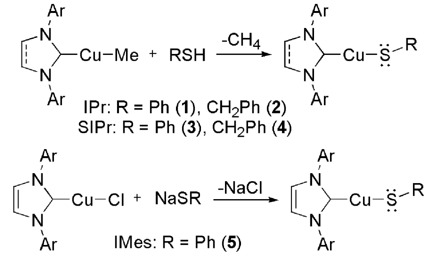
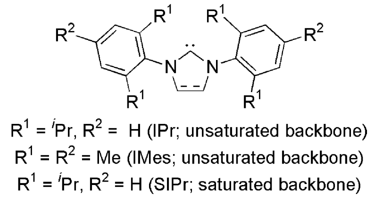


Chart 1. Depiction of NHC Ligands Used in This Study



the IPr or SIPr ligand (Scheme 1). We have isolated and fully characterized five new monomeric copper(I) thiolate compounds: (IPr)Cu(SPh) (**1**), (IPr)Cu(SCH$_2$Ph) (**2**), (SIPr)-Cu(SPh) (**3**), (SIPr)Cu(SCH$_2$Ph) (**4**), and (IMes)Cu(SPh) (**5**). (IMes)Cu(SCH$_2$Ph) (**6**) has been generated in situ (NMR tube experiments), but attempts to cleanly isolate this complex have failed. Complexes **1**−**4** are isolated in 79−84% yield, and **5** is isolated in 75% yield after the reaction of (IMes)-CuCl with [Na][SPh].

There are few examples of solid-state structures of copper thiolate complexes.[29−32] Single crystals of **1**−**5** suitable for X-ray diffraction study were obtained. ORTEPs of **1**−**4** are shown in Figures 1−4, respectively (details of **5** are provided in the Supporting Information). All of the structures reveal monomeric complexes with nearly linear geometries about the Cu center, with C1−Cu1−S1 bond angles ranging from 169.5(1)° for **4** to 178.3(1)° for **1**. There is little electronic effect on the Cu−S bond distances due to saturation/unsaturation of the NHC backbone with similar Cu−S bond distances of 2.139(1) and 2.145(1) Å for **1** and **3**, respectively, and 2.127(1) and 2.121(1) Å for **2** and **4**, respectively. The Cu1−C1 bond distances are statistically equivalent for **1**−**4** ranging from 1.895(4) to 1.898(2) Å. The S1−C28 bond lengths of the phenyl thiolates are slightly shorter than those of the benzyl thiolates [1.779(2) Å for **1** compared to 1.835(4) Å for **2** and 1.765(4) Å for **3** compared to 1.810(6) Å for **4**].

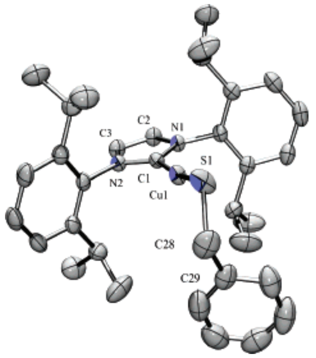


Figure 2. ORTEP of (IPr)Cu(SCH$_2$Ph) (**2**) (30% probability; H atoms omitted). Selected bond distances (Å): Cu1−C1 1.898(2), Cu1−S1 2.127-(1), S1−C28 1.835(4). Selected bond angles (deg): C1−Cu1−S1 171.5-(1), C28−S1−Cu1 112.1(1), N2−C1−Cu1 129.4(2), N1−C1−Cu1 127.1-(2), C29−C28−S1 117.7(3).

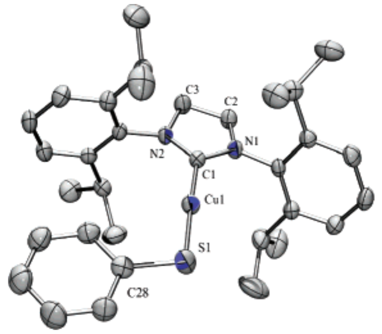


Figure 3. ORTEP of (SIPr)Cu(SPh) (**3**) (30% probability; H atoms omitted). Selected bond distances (Å): Cu1−C1 1.896(3), Cu1−S1 2.145(1), S1−C28 1.765(4). Selected bond angles (deg): C1−Cu1−S1 177.5(1), C28−S1−Cu1 105.8(1), N2−C1−Cu1 127.1(2), N1−C1−Cu1 124.9(2).

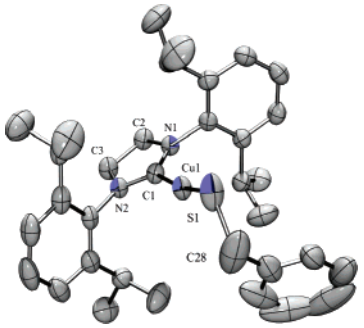


Figure 4. ORTEP of (SIPr)Cu(SCH$_2$Ph) (**4**) (30% probability; H atoms omitted). Selected bond distances (Å): Cu1−C1 1.897(3), Cu1−S1 2.121-(1), S1−C28 1.810(6). Selected bond angles (deg): C1−Cu1−S1 169.5-(1), C28−S1−Cu1 110.9(3), N2−C1−Cu1 127.8(2), N1−C1−Cu1 124.9-(2), C29−C28−S1 117.6(3).

Catalytic hydrothiolation of a range of electron-deficient olefins was attempted using **1**−**5** as catalysts. Both arenethiols (benzenethiol) and alkanethiols (benzylmercaptan) are successfully added to mono-, di-, and trisubstituted olefins. Table 1 depicts representative results using 5 mol % of Cu catalyst. All reactions are 100% regioselective (by ^{1}H NMR

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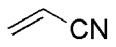
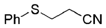
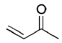
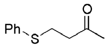
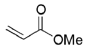
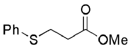
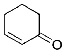
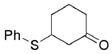
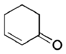
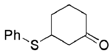
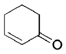
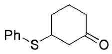
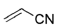
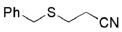
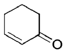
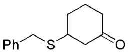
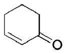
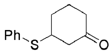
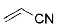
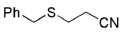
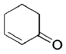
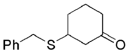
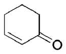
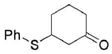
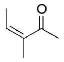
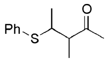
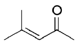
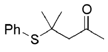
Table 1. Results of Cu^{I}-Catalyzed Hydrothiolation of Electron-Deficient Olefins[a]

[Cu]	nucleophile	olefin	temp (°C)	time	product	% conversion[b]	control[c]
1	PhSH		rt	3.5 h		>95	90h, <5%
1	PhSH		rt	5 min		>95	2h, 32%
1	PhSH		rt	0.5 h		>95	24h, <5%
1	PhSH		rt	8 h		>95	24h, <5%
1[d]	PhSH		rt	29 h		>95	24h, <5%
1[e]	PhSH		80	32 h		>95	24h, <5%
2	PhCH$_2$SH		rt	2 h		>95	41h, <5%
2	PhCH$_2$SH		rt	2 h		>95	17h, <5%
3	PhSH		40	16.5 h		>95	24h, <5%
4	PhCH$_2$SH		60	4 h		>95	41h, <5%
4	PhCH$_2$SH		rt	8.5 h		>95	17h, <5%
5	PhSH		rt	5 min		>95	24h, <5%
5	PhSH		rt	2 h		>95 (79%)[f]	2h, <5%
5	PhSH		rt	2 h		>95	2h, <5%

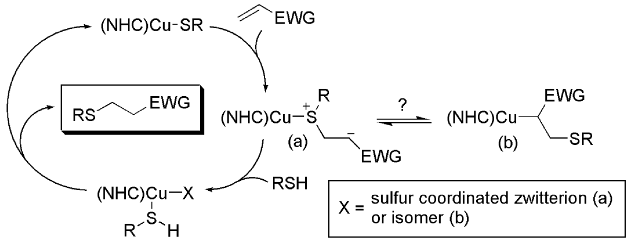
[a] All reactions have 5 mol % [Cu] in C_6D_6. [b] Determined by ^{1}H NMR spectroscopy. [c] In the absence of (NHC)Cu(SR) catalyst. [d] 1 mol % **1**. [e] 0.1 mol % **1**. [f] Isolated yield.

spectroscopy) for the "anti-Markovnikov" product, and most conversions occur relatively rapidly at room temperature.

Comparisons of control reactions in the absence of Cu catalyst to Cu-catalyzed variants clearly indicate the important role of the (NHC)Cu(SR) systems. For example, all of the Cu-catalyzed reactions go to >95% completion, and most do so in a few hours or, in some cases, in minutes. In contrast, with one exception, under identical conditions, the uncatalyzed reactions do not produce detectable quantities of products after prolonged reaction times. The only uncatalyzed reaction that results in hydrothiolation is the combination of benzenethiol and methyl vinyl ketone. For these substrates, the Cu-catalyzed reaction is complete after 5 min, while the uncatalyzed reaction is 32% converted after 2 h.

In order to determine the impact of the NHC ligand, we compared the catalytic addition of benzenethiol to cyclohexenone. At room temperature, the IMes complex **5** catalyzes this reaction to completion in less than 5 min. In comparison, the IPr complex **1** requires 8 h to enact complete conversion. Thus, the less sterically bulky (IMes)Cu catalyst is at least 2 orders of magnitude more active. For this same reaction using (SIPr)Cu(SPh) (**3**) as the catalyst, >95% conversion is detected after 16.5 h at a temperature of 40 °C. The reaction with **3** is much slower, but the low solubility of the (SIPr)Cu catalyst likely contributes to the reduced rate. In order to probe reduced catalyst loadings, we tested the reaction of benzenethiol and 1,4-cyclohexenone with 1 and 0.1 mol % of complex **1**. The reaction with 1 mol % of **1** requires 29 h to reach >95% conversion at room temperature, while the reaction with 0.1 mol % of **1** (80 °C) reaches >95% conversion after 32 h. These results demonstrate that low catalyst loadings are feasible. For the reaction of benzenethiol and (*E*)-3-methyl-3-penten-2-one, we have demonstrated facile isolation of the new organic product 3-methyl-4-(thiophenyl)-2-pentanone as predominantly one diastereomer (>90% selective) in 79% yield.

Scheme 2. Possible Mechanism for the Cu-Catalyzed Hydrothiolation of Olefins (EWG = Electron Withdrawing Group)



For the catalytic hydroamination and hydroalkoxylation of electron-deficient olefins using (NHC)Cu(NHR) and (NHC)Cu(OR) systems, we have tentatively proposed a mechanism that involves intermolecular nucleophilic addition of the amido or alkoxo ligand to free olefin.[22] The observed hydrothiolation reactions may proceed by this pathway, where the thiolate ligand initiates nucleophilic addition to the more electrophilic β-C of the C=C bond to form a *S*-coordinated zwitterion (Scheme 2). The zwitterion can then rearrange to form the C-bound isomer and/or bind another equiv of thiol. Following proton transfer, release of the organic product regenerates the catalyst. Consistent with this suggestion, catalytic cycles that incorporate benzyl thiolate are more rapid than those that incorporate the less nucleophilic benzenethiol. In addition, hydrothiolation reactions are more rapid than corresponding hydroaryloxylation or hydroalkoxylation transformations.

In summary, new monomeric copper(I) thiolate complexes have been synthesized, isolated, and demonstrated to catalyze the hydrothiolation of electron-deficient olefins with "anti-Markovnikov" selectivity. Although S−H addition to olefins catalyzed by simple bases is possible, our systems offer the possibility of varying the ancillary ligand to increase activity, access functional group tolerance, and control stereoselectivity.

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Supporting Information Available: Details of synthesis and characterization, complete tables of crystal data, collection and refinement data, atomic coordinates, bond distances and angles and anisotropic displacement coefficients for complexes **1**−**5**, and ^{1}H NMR spectra of catalytic reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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