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Catalytic Production of Isothiocyanates via a Mo(II)/Mo(IV) Cycle for the "Soft" Sulfur Oxidation of Isonitriles

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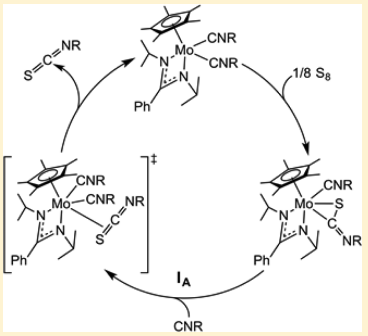
Supporting Information

ABSTRACT: In the presence of excess amounts of elemental sulfur, the dimolybdenum dinitrogen complex $\{Cp^*Mo[N(^iPr)C(Ph)N(^iPr)]\}_2(\mu\text{-}N_2)$ (**4**; $Cp^* = \eta^5\text{-}C_5Me_5$) serves as a precatalyst for the production of isothiocyanates from isonitriles via highly efficient and atom-economical metal-mediated sulfur atom transfer (SAT) under mild conditions. Mechanistic and structural studies support a catalytic cycle for SAT involving initial formation of a Mo(II) bis(isonitrile) complex that then undergoes sulfination to generate a formal "side-bound" Mo(IV) κ^2-(*C*,*S*)-isothiocyanate as the key intermediate. This metal-catalyzed SAT process has further been employed for the "on-demand" production of isothiocyanates that are trapped in situ by benzhydrazides to provide thiosemicarbazides, which are useful precursors to biologically active thiadiazoles.



INTRODUCTION

One of the primary tenets of "green" chemistry is to develop new atom-economical and energy-efficient industrial processes that contribute to reducing the environmental impact associated with production of commodity and fine chemicals.[1] In this regard, organic isothiocyanates RN═C═S (ITCs) are a valuable class of synthetic building blocks for the assembly of more complex sulfur- and nitrogen-containing molecular frameworks.[2] Methyl isothiocyanate (MITC), which is the most industrially significant member of this family, is produced on the multikiloton scale through thermal rearrangement of methyl thiocyanate, which is obtained itself through methylation of thiocyanate anion.[2,3] Other alkyl and aryl isothiocyanates, however, have often been prepared through the traditional route of reacting an amine with thiophosgene (Cl_2CS).[4] In order to avoid use of the latter volatile and toxic reagent, other synthetic methods have been developed that involve a variety of different thiocarbonyl transfer reagents.[5] Nonetheless, there still remains the need to develop new synthetic routes to ITCs that (a) offer a broader scope of functional group tolerance, (b) can be derived from inexpensive and nontoxic starting materials, and (c) are suitable for being employed for the "on-demand" in situ generation of ITCs as a means by which to avoid the large-scale handling and storing of these compounds, which are also known to pose serious health and environmental risks. With respect to point b, elemental sulfur (hereafter referred to as S_8) is an intriguing raw material to consider as a readily available feedstock. since the world's annual production is in excess of 70 million metric tons.[6] Marks and co-workers[7] have also recently drawn attention to the use of sulfur as a "soft" oxidant as a strategy for increasing the selectivity of a chemical process in which more complex product mixtures arise when molecular oxygen (O_2) is employed instead. Indeed, several groups of investigators have now reported the direct synthesis of ITCs through sulfination of isonitriles (RN≡C) with S_8 using either transition-metal complexes or, in one example, selenium as a catalyst.[8−12] For transition-metal catalysts, elucidating the steric and electronic requirements for key sulfur atom transfer (SAT) processes between S_8 and the RNC substrate can potentially lead to more optimal reaction conditions (e.g., time and temperature) and higher yields, as well as a larger range of ITCs and products derived therefrom.

Previously, we have demonstrated that group 6 metal complexes supported by the monocyclopentadienyl, monoamidinate (CPAM) ligand framework are capable of catalyzing the production of organic isocyanates RN═C═O from isonitriles through use of either nitrous oxide (N_2O) or carbon dioxide (CO_2) via oxygen-atom transfer (OAT) or, alternatively, from organic azides (RN_3) through nitrene group transfer (NGT) to carbon monoxide (CO).[13−15] In each case, the overall catalytic cycle proceeds through a formal midvalent M(II)/M(IV) redox couple. More recently, we extended these studies to explore the possibility of developing SAT processes that can be mediated by CPAM molybdenum complexes. Gratifyingly, these studies led to the establishment of a photocatalytic cycle for generation of carbonyl sulfide (S═C═O, also known as COS) from CO and S_8 under near-ambient conditions.[16] Notably, when the reactions were conducted in the presence of primary amines, a variety of symmetric 1,3-disubstituted ureas ($(RNH)_2CO$) were obtained in excellent yields, thereby validating this system for the "on-demand" (in situ) generation of COS. Herein, we now report the successful catalytic synthesis of several ITCs from S_8 and the corresponding isonitriles that proceeds under near-ambient

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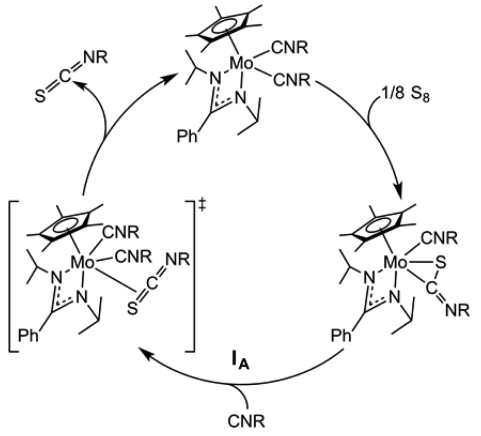
conditions according to the proposed Mo(II)/Mo(IV) cycle of Scheme 1, which is supported by the isolation and structural

Scheme 1

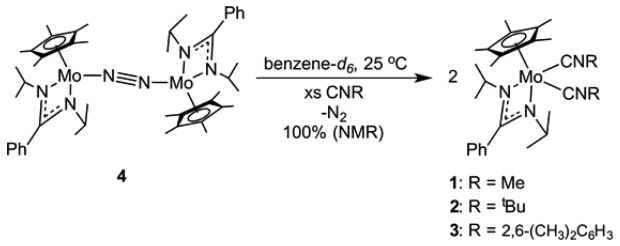


characterization of key intermediates. Importantly, this catalytic process is uninhibited by the presence of benzhydrazide derivatives, which provides access to the one-pot synthesis of several thiosemicarbazides in high yield through a similar on-demand generation of ITCs. Thiosemicarbazides are, in turn, important precursors to a range of biologically active thiadiazoles.[17]

RESULTS AND DISCUSSION

Catalyst Synthesis and SAT Reactions. As Scheme 2 reveals, the CPAM Mo(II) bis(isonitrile) complexes Cp*Mo-

Scheme 2



$[N(^{i}Pr)C(Ph)N(^{i}Pr)](CNR)_2$ (Cp* = η^5-C_5Me_5; R = Me (**1**), ^{t}Bu (**2**), 2,6-$(CH_3)_2C_6H_3$ (**3**)) were conveniently prepared in high yield through ligand substitution of dinitrogen (N_2) in the dinuclear dinitrogen complex $\{Cp^*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)]\}_2(\mu\text{-}\eta^1\text{:}\eta^1\text{-}N_2)$ (**4**)[18] by the corresponding isonitriles.[19] A solid-state structural characterization of **1** (ν_{CN} 2086, 1767 cm^{-1}), achieved through single-crystal X-ray analysis, revealed a sharp geometric difference between the two methyl isocyanide ligands, with one bound to the molybdenum center in a nearly linear fashion and the other being distinctly nonlinearly ligated (cf. Mo−C−N bond angles of 166.9(2) and 129.6(2)°, respectively).[19] A similar structural feature was previously reported for a closely related structural analogue of **3**,[18] and collectively, these solid-state data support the conclusion that there exists a substantial degree of π back-bonding[20] between the metal center and the isonitrile ligands in **1**−**3**. Finally, it can be noted that, in solution, ^{1}H NMR spectra support a C_s-symmetric structure for all three compounds in which the isonitrile ligands are magnetically and, presumably, chemically equivalent.[19]

As illustrated by the stacked plot of partial ^{1}H NMR spectra displayed in Figure 1, addition of excess equivalents of an

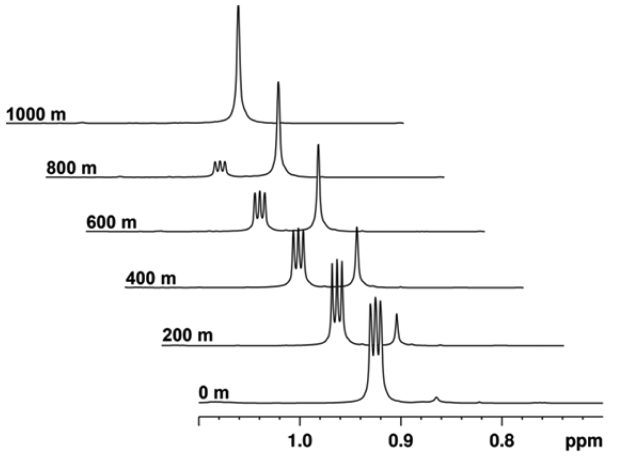


Figure 1. Partial ^{1}H NMR (400 MHz, 50 °C, benzene-d_6) spectra for production of ^{t}BuNCS (singlet) from ^{t}BuNC (triplet) in the presence of **2** (5 mol %, c = 8.3 mM) and excess S_8. Spectra were recorded every 200 min and vertically displayed (t = 0 min at bottom) with a horizontal offset of 0.02 ppm.

isonitrile and S_8 to benzene-d_6 solutions of **1**−**3** (generated in situ from **4**) led to steady generation of the corresponding ITCs over time. For methyl and *tert*-butyl isonitrile (MeNC and ^{t}BuNC, respectively), this reaction occurred readily at room temperature, and it was further accelerated upon heating (cf. TOF = 1.2 h^{-1} at 50 °C for ^{t}BuNC; Figure 1). In the case of 2,6-dimethylphenyl isonitrile, however, an elevated temperature of 80 °C was essential to observe catalytic turnover.[19]

Importantly, these isonitrile sulfination reactions were found to be unaffected by the use of solvents that had not been previously dried by standard procedures, thereby demonstrating a tolerance of the catalytic process to trace amounts of moisture.

Mechanistic Investigations. Due to experimental difficulties in establishing the exact nature of elemental sulfur speciation and of intermediates that are involved, reports for metal-mediated SAT processes are oftentimes sparse with respect to mechanistic details.[9,11] With these challenges in mind, we undertook a series of investigations that would serve to put the observed catalytic SAT process of Figure 1 onto a firm mechanistic foundation. Thus, to begin, following the course of isonitrile sulfination as catalyzed by the complexes **1**−**3** showed, in each case, the appearance of only a single new CPAM-based molybdenum complex. Fortunately, efforts to structurally characterize this set of new species, hereafter referred to as complexes **5**−**7**, were successful. More specifically, as Scheme 3 reveals, addition of S_8 to benzene-d_6 solutions of **1**−**3**, in the absence of any additional isonitrile, quantitatively generated previously observed **5**−**7** as determined by ^{1}H NMR spectroscopy. Unfortunately, subsequent attempts to isolate these compounds in pure form only resulted in their decomposition. On the other hand, by switching to toluene as the solvent, addition of S_8 to a solution of **2** (generated in situ from **4** and 4 equiv of ^{t}BuNC), followed by immediate removal of solids by filtration, layering the toluene filtrate with pentane, and cooling to −30 °C, yielded single

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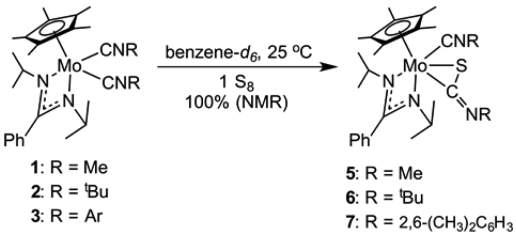
Scheme 3



1: R = Me
2: R = ^{t}Bu
3: R = Ar

5: R = Me
6: R = ^{t}Bu
7: R = 2,6-$(CH_3)_2C_6H_3$

crystals of compound **6** that were suitable for structure determination by X-ray crystallography.[16] Figure 2 presents

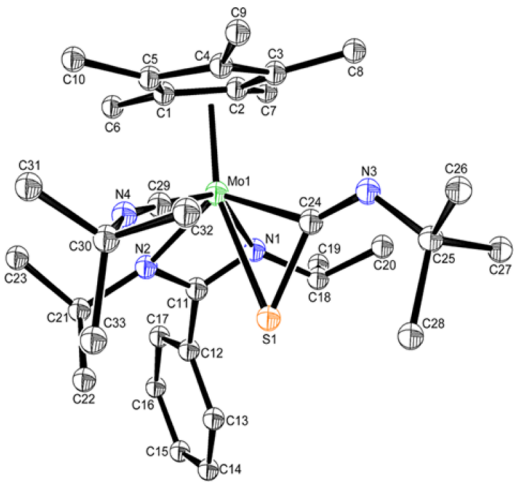


Figure 2. Molecular structure (30% thermal ellipsoids) of compound **6**. Hydrogen atoms have been removed for the sake of clarity. Selected bond lengths (Å) and angles (deg): Mo1−S1 2.4976(6), Mo1−C24 2.117(2), S1−C24 1.776(2), C24−N3 1.255(2), N3−C25 1.490(3), Mo1−C29 2.050(2), C29−N4 1.168(3), N4−C30 1.455(3); S1−C24−N3 136.91(18), Mo1−C24−N3 143.51(17), C24−N3−C25 125.8(2), Mo1−C29−N4 178.23(17), C29−N4−C30 159.5(2).

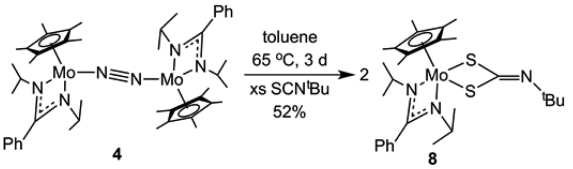
the solid-state molecular structure obtained from this analysis, along with selected geometric parameters, that serve to establish **6** as being the complex Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)](CN^{t}Bu)[κ-(*S*,*C*)-SCN^{t}Bu], depicted in Scheme 3. To the best of our knowledge, **6** is not only a very rare example of a formal "side-bound" κ-(*S*,*C*)-isothiocyanate transition-metal complex, but it is the only one that has been obtained through the direct sulfination of a metal-bound isonitrile ligand and the first to involve a midvalent Mo(IV) center.[21] On the basis of similarities in NMR data and chemical reactivity, vis-à-vis the catalytic conversion of RNC to RNCS with S_8, it is reasonable to assume that compounds **5** and **7** share the same structure as **6**. Finally, it can be noted that, in solution, **5**−**7** all appear to engage in structural dynamics that give rise to a time-averaged C_s-symmetric molecular structure.[19]

Additional insight regarding the most probable mechanism for the sulfination of isonitriles as catalyzed by **1**−**3** was obtained by a variable-temperature ^{1}H NMR Eyring analysis employing **2** as the catalyst for the conversion of ^{t}BuNC to ^{t}BuNCS under pseudo-first-order conditions with respect to S_8.[19] We recognize from the outset that results obtained from such a study are less than ideal since the exact speciation and concentration of sulfur in solution, as well as the nature of the intermediate involved in the intimate transfer of a single sulfur atom from elemental sulfur to **2**, are not known. However, as a guide for thought, this study provided estimates for the enthalpy and entropy of activations of $\Delta H^{\ddagger}$ = 17.8 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −13.2 cal mol^{-1} K^{-1}, respectively, and these values correspond to a calculated $\Delta G^{\ddagger}$ = 22.3 kcal mol^{-1} at a temperature of 298 K. The negative value for $\Delta S^{\ddagger}$ also implies that a more highly ordered transition state for the rate-determining step (RDS) in the catalytic cycle exists. Since **6** is the only observed intermediate, one possible scenario is that this RDS corresponds to a formal associative interchange ($\mathbf{I_A}$) mechanism[22] in which coordination of ^{t}BuNC to **6** proceeds simultaneously with formal reductive elimination and release of free ^{t}BuNCS to regenerate **2**.

The overall proposed SAT catalytic cycle of Scheme 1 proceeds via a formal Mo(II)/Mo(IV) oxidation couple, and this is in keeping with previous results obtained by us for catalytic OAT chemistry mediated by similar CPAM group 6 complexes.[13−15] It is interesting then to compare the mechanism of Scheme 1 to that of Bargon and co-workers,[11a] who have proposed a different catalytic cycle which is based on a Mo(IV)/Mo(VI) oxidation couple to account for the sulfination of isonitriles to ITCs that is mediated by the Mo(IV) oxo bis(dithiocarbamate) Mo(O)[κ-(*S*,*S*)-S_2CN(Et$_2$)]$_2$ (**I**). As proposed by these authors, a key intermediate in the SAT cycle is reaction of **I** with S_8 to produce the Mo(VI) persulfido complex Mo(O)(η^2-S_2)[κ-(*S*,*S*)-S_2CN(Et$_2$)]$_2$ (**II**), which then transfers a sulfur atom to an isonitrile to produce the Mo(VI) terminal sulfide Mo(O)(S)[κ-(*S*,*S*)-S_2CN(Et$_2$)]$_2$ (**III**). Although **III** must ultimately cycle back to **I** through reductive transfer of another sulfur atom to an isonitrile to generate another 1 equiv of ITC, no mechanistic considerations were provided to illuminate how this latter step might occur. Intriguingly, we have also observed and isolated the CPAM Mo(IV) carbonyl persulfido complex Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)](CO)(η^2-S_2) (**IV**) and the dimolybdenum disulfide {Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)]}$_2$(μ-S)$_2$ (**V**), which are key intermediates in the photocatalytic sulfination of CO by S_8.[16] However, in the present work, no evidence has yet been found for the corresponding Mo(IV) isonitrile persulfido intermediate Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)](CNR)(η^2-S_2) (**VI**) or for the intermediacy of **V**.[23] Thus, although there are additional details that could be filled in, the catalytic cycle of Scheme 1 is attractive for its mechanistic simplicity with respect to sulfur atom economy and a minimal number of formal metal oxidation/reduction steps.

One curious observation is that the intermediates involved in the catalytic cycle of Scheme 1 also appear to be impervious to a steady buildup in concentration of the ITC product, which a priori one might have thought could productively compete for coordination to Mo(II) centers. Indeed, as Scheme 4 reveals, treatment of a toluene solution of **4** with excess amounts of ^{t}BuNCS at the slightly elevated temperature of 65 °C provided a good yield of the CPAM Mo(IV) dithiocarbonimidate Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)][κ-(*S*,*S*)-S_2C-(N^{t}Bu)] (**8**) as an orange crystalline material.[19] The solid-state molecular

Scheme 4



4 **8**

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structure of **8** as determined by single-crystal X-ray analysis is presented in Figure 3, for which the geometric bond length

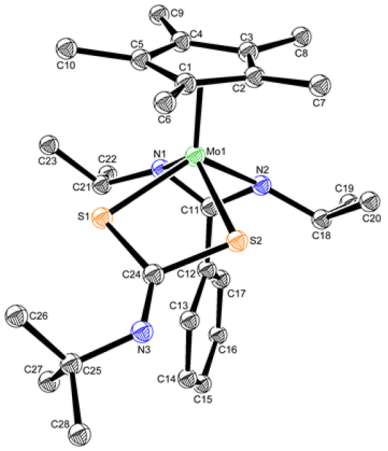
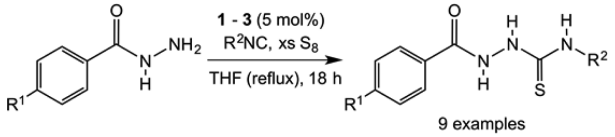


Figure 3. Molecular structure (30% thermal ellipsoids) of compound **8**. Hydrogen atoms have been removed for the sake of clarity. Selected bond lengths (Å) and angles (deg): Mo1−S1 2.3694(4), Mo1−S2 2.3763(3), S1−C24 1.7963(12), S2−C24 1.7823(12), C24−N3 1.2631(15), N3−C25 1.4850(16); S1−C24−N3 133.89(9), S2−C24−N3 122.78(9), C24−N3−C25 123.26(10).

values (Å) associated with the κ-(*S*,*S*)-S_2CN^tBu fragment are as follows: Mo1−S1, 2.3694(4); Mo1−S2, 2.3763(3); S1−C24, 1.7832(12); S2−C24, 1.7963(12); C24−N3, 1.2631(15).[24] On the basis of literature precedent, the most likely mechanism for formation of **8** involves SAT from initial coordination of ^{t}BuNCS to a Mo(II) center to form a transient formal Mo(IV) terminal sulfide through elimination of ^{t}BuNC, followed by trapping of this metal sulfide with another 1 equiv of ^{t}BuNCS to form the final thermodynamically stable dithiocarbonimidate product.[25] Thus, the fact that **8** is never observed during conversion of ^{t}BuNC and S_8 to ^{t}BuNCS strongly suggests the absence of competing SAT processes involving the ITC product that might lead to CPAM Mo^{IV}(S) intermediates during catalysis.

"On-Demand" ITC Production. Given the known potential hazards of working with isolated quantities of ITCs, we next sought to apply the new catalytic SAT process for preparative-scale synthetic purposes. In this regard, trapping of the ITC intermediate through addition of a benzhydrazide to form a thiosemicarbazide product according to Scheme 5 is a

Scheme 5



very attractive target.[26] Gratifyingly, as Scheme 5 and Table 1 reveal, in refluxing THF, compound **4** is indeed capable of serving as an efficient precatalyst for the desired coupling chemistry to provide a number of thiosemicarbazides in excellent yields.[19] Finally, it is important to note that, while it has been recently reported that thioureas $(R^1NH)C(S)(NHR^2)$ can be conveniently synthesized directly by heating a mixture of elemental sulfur, an amine (R^1NH_2), and an isonitrile (R^2NC),[10d] in our hands, this procedure does not appear to be competent for the analogous production of thiosemicarbazides from acyl hydrazides.

Table 1. Synthesis of Thiosemicarbazides via in Situ Generation of Isothiocyanates According to Scheme 5

R^1	R^2	yield (%)	R^1	R^2	yield (%)
H	Me	76	Me	Ar[a]	95
H	^{t}Bu	69	OMe	Me	82
H	Ar[a]	88	OMe	^{t}Bu	80
Me	Me	96	OMe	Ar[a]	91
Me	^{t}Bu	97			

[a]Ar = 2,6-$(CH_3)_2C_6H_3$.

CONCLUSIONS

In conclusion, the present report serves to establish a new class of earth-abundant transition-metal catalysts that can be used to take advantage of inexpensive and abundant elemental sulfur for the production of synthetically useful ITC compounds. Through spectroscopic analyses and the isolation and structural characterization of a key catalytic intermediate, support for the proposed Mo(II)/Mo(IV) mechanism of Scheme 1 is presented. Additional studies are currently in progress to extend the catalytic utility of CPAM group 6 metal complexes.

EXPERIMENTAL SECTION

General Considerations. All manipulations with air- and moisture-sensitive compounds were carried out under N_2 or Ar atmospheres using standard Schlenk or glovebox techniques. Et_2O and THF were dried over Na/benzophenone and distilled under N_2 prior to use. Toluene and pentane were dried and deoxygenated by passage over activated alumina and GetterMax 135 catalyst (purchased from Research Catalysts, Inc.) and collected under N_2 prior to use. Benzene-d_6 was dried over Na/K alloy and isolated by vacuum transfer prior to use, except when otherwise stated. Celite was oven-dried (150 °C for several days) before use in the glovebox. Cooling was performed in the internal freezer of a glovebox maintained at −30 °C. *tert*-Butyl isonitrile was purchased from Sigma-Aldrich and degassed by three "freeze−pump−thaw" cycles prior to use. *tert*-Butyl isothiocyanate was dried over CaH_2 and isolated by vacuum transfer prior to use. 2,6-Dimethylphenyl isonitrile, methyl triflate, and all benzhydrazides were purchased from Sigma-Aldrich and used as received. Elemental sulfur was purchased from Fischer Scientific and used as received. Methyl isonitrile[27] and compound **4**[18] were prepared according to the literature in similar yield and purity. ^{1}H NMR spectra were recorded at 400 or 500 MHz. ^{13}C NMR spectra were recorded at 125 MHz. Elemental analyses were carried out by Midwest Microlab LLC.

Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)](CNCH$_3$)$_2$ (1). Methyl isonitrile (0.01 mL, 0.19 mmol) was added via microsyringe to a solution of **4** (0.038 g, 0.04 mmol) in 3 mL of toluene at room temperature. The resulting red solution was stirred for 1 h, at which point volatiles were removed in vacuo. The resulting red solid was extracted into pentane and filtered through a pad of Celite, the volume was reduced in vacuo, and the resulting solution was cooled to −30 °C overnight, furnishing red crystals of **1** (0.037 g, yield 85%). Data for **1** are as follows. Anal. Calcd for $C_{27}H_{40}N_4Mo$: C, 62.76; N, 7.81; H, 10.85. Found: C, 63.09; N, 7.57; H, 10.79. ^{1}H NMR (400 MHz, benzene-d_6): 1.07 [6H, d, J = 6.4 Hz, $CH(CH_3)_2$], 1.15 [6H, d, J = 6.4 Hz, $CH(CH_3)_2$], 1.95 [15H, s, $C_5(CH_3)_5$], 3.41 (6H, s, $CNCH_3$), 3.55 [2H, sp, J = 6.4 Hz, $CH(CH_3)_2$], 7.05 (2H, m, C_6H_5), 7.16 (2H, m, C_6H_5), 7.23 (1H, d, J = 7.4 Hz, C_6H_5). IR (KBr) ν_{CN} 2086, 1767 cm^{-1}.

Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)](CN^{t}Bu)(η^2-SCN^{t}Bu) (6). To a solution of **2** (0.06 mmol generated in situ) in 2 mL of toluene was added S_8 (0.014 g, 0.06 mmol) at room temperature. The resulting red solution was stirred for 10 min, at which point solids were removed by filtration through Celite and volatiles were removed in vacuo to leave a red oil, which was analyzed by ^{1}H NMR (confirming it to be analogous to the

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catalyst resting state; see the Supporting Information). Crystalline **6** was obtained cooling a toluene solution to −30 °C and then layering pentane on top to diffuse in to yield single crystals suitable for X-ray analysis (vide infra). Due to its instability, larger amounts of crystalline material suitable for further analysis of **6** could not be obtained by this procedure.

Cp*Mo[N(^{i}Pr)C(Ph)N(^{i}Pr)](κ-(*S,S*)-S_2CN^{t}Bu) (8). To a solution of **4** (0.042 g, 0.05 mmol) in 10 mL of toluene in a 100 mL Schlenk tube was added *tert*-butyl isothiocyanate (0.06 mL, 0.47 mmol). The tube was sealed, and the solution was stirred at 65 °C for 3 days, at which point volatiles were removed in vacuo. The resulting orange-red oil was extracted in pentane, filtered through Celite, concentrated, and cooled to −30 °C to yield orange-red crystals of **8** (0.028 g, 52% yield). Data for **8** are as follows. Anal. Calcd for $C_{28}H_{43}N_3S_2Mo$: C, 57.81; N, 7.23; H, 7.46. Found: C, 58.17; N, 7.29; H, 7.39. ^{1}H NMR (400 MHz, benzene-d_6): 0.93 [3H, d, J = 6.4 Hz, CH(CH_3)$_2$], 0.95 [3H, d, J = 6.4 Hz, CH(CH_3)$_2$], 1.27 [3H, d, J = 6.4 Hz, CH(CH_3)$_2$], 1.27 [3H, d, J = 6.4 Hz, CH(CH_3)$_2$], 1.83 [15H, s, C_5(CH_3)$_5$], 1.84 [9H, s, S_2CNC(CH_3)$_3$], 3.37 [1H, sp, J = 6.4 Hz, CH(CH$_3$)$_2$], 3.38 [1H, sp, J = 6.4 Hz, CH(CH$_3$)$_2$], 6.94 (4H, m, C_6H_5), 7.11 (1H, m, C_6H_5).

Variable-Temperature NMR Experiments. A representative procedure is given. In a J. Young NMR tube equipped with a Teflon valve was added 0.6 mL of benzene-d_6 solution consisting of **2** (prepared in situ) (8.6 mM, 5 μmol), *tert*-butyl isonitrile (171.6 mM, 103 μmol), and durene internal standard (35.9 mM, 22 μmol). S_8 (0.026 g, 102 μmol) was added, and the tube was quickly placed into the NMR probe, which was pre-equilibrated to 50 °C. NMR spectra were recorded every 10 min until all *tert*-butyl isonitrile was consumed. The concentration of *tert*-butyl isothiocyanate was plotted versus time and fit with a first-order polynomial, affording the initial rate constant as the slope.

Synthesis of Thiosemicarbazides through "On-Demand" Generation of Isothiocyanates. A representative procedure is given. In 3 mL of THF, **2** (8 μmol) was generated in situ through addition of 44 equiv of *tert*-butyl isonitrile (20 μL, 0.177 μmol) with respect to to **4** (0.004 g, 0.004 μmol). After 30 min, excess S_8 (0.040 g, 0.155 μmol) and *p*-tolylbenzhydrazide (0.020 g, 0.131 μmol) were added with an additional 5 mL of THF. The solution was heated to 85 °C in a sealed Schlenk tube for 16 h, after which volatiles were removed in vacuo. The organic product was extracted into ethyl acetate and then washed with 1 M HCl and 1 M KCl. The organic layer was isolated and passed through a pad of silica gel supported by a Kimwipe within a glass pipet. Volatiles were removed in vacuo to furnish 1-(*p*-tolylbenzoyl)-4-*tert*-butylthiosemicarbazide as brown crystals (0.032 g, 97% yield). Characterization (^{1}H NMR, ^{13}C{^{1}H} NMR, and ESI-MS) data and yields are provided in the Supporting Information for all thiosemicarbazides.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00302.

Supporting spectra, characterization data, and crystal data (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Sustainable Industrial Chemistry. Principles, Tools and Industrial Examples*; Cavani, F., Centi, G., Perathoner, S., Trifiro, F., Eds.; Wiley-VCH: Weinheim, Germany, 2009.

(2) Romanowski, F.; Klenk, H. Thiocyanates and Isothiocyanates. In *Ulmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.

(3) (a) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1880**, *13*, 1349−1352. (b) Fava, A. In *The Chemistry of Organic Sulfur Compounds*; Kharasch, N., Meyers, C. Y., Eds.; Pergamon Press: New York, 1966; Vol. *2*, pp 73−91.

(4) Dyer, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 777−787.

(5) See, for instance: (a) Moore, M. L.; Crossley, F. S. Methyl Isothiocyanate. *Org. Synth.* **1941**, 599. (b) Hodgkins, J. E.; Reeves, W. P. *J. Org. Chem.* **1964**, *29*, 3098−3099. (c) L'Abbe, G. *Synthesis* **1987**, *1987*, 525−531. (d) Zhang, X.; Lee, Y. K.; Kelley, J. A.; Burke, T. R., Jr. *J. Org. Chem.* **2000**, *65*, 6237−6240. (e) Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969−3971. (f) Li, Z.-Y.; Ma, H.-Z.; Han, C.; Xi, H.-T.; Meng, Q.; Chen, X.; Sun, X.-Q. *Synthesis* **2013**, *45*, 1667−1674.

(6) (a) Meyer, B. *Chem. Rev.* **1976**, *76*, 367−388. (b) Nehb, W.; Vydra, K. Sulfur. In *Ulmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2006. (c) Kutney, G. *Sulfur: History, Technology, Applications & Industry*, 2nd ed.; ChemTec Publications: Toronto, 2013. (d) Donahue, J. P. *Chem. Rev.* **2006**, *106*, 4747−4783.

(7) (a) Zhu, Q.; Wegener, S. L.; Xie, C.; Uche, O.; Neurock, M.; Marks, T. J. *Nat. Chem.* **2013**, *5*, 104−109. (b) Peter, M.; Marks, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15234−15240.

(8) For reviews of transition-metal-catalyzed processes involving isonitriles, see: (a) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F.-Q.; Mohan, R.; Ravindra, M. P.; Shah, D.; Yang, X.; Fleming, F. F. *Adv. Synth. Catal.* **2014**, *356*, 2135−2196. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698−2779.

(9) For reviews of transition-metal-catalyzed SAT processes, see: (a) Adam, W.; Bargon, R. M. *Chem. Rev.* **2004**, *104*, 251−261. (b) Arisawa, M.; Yamaguchi, M. *Pure Appl. Chem.* **2008**, *80*, 993−1003.

(10) For examples of non-metal-catalyzed SAT processes employing S_8, see: (a) Nguyen, T. B.; Ermolenko, L.; Dean, W. A.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 5948−5951. (b) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 4274−4277. (c) Nguyen, T. B.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2014**, *16*, 310−313. (d) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Synthesis* **2014**, *46*, 3172−3179.

(11) For transition-metal-catalyzed syntheses of ITCs using S_8 and RNC, see: (a) Adam, W.; Bargon, R. M.; Bosio, S. G.; Schenk, W. A.; Stalke, D. *J. Org. Chem.* **2002**, *67*, 7037−7041. (c) Arisawa, M.; Ashikawa, M.; Suwa, A.; Yamaguchi, M. *Tetrahedron Lett.* **2005**, *46*, 1727−1729.

(12) For non-metal-catalyzed syntheses of ITCs using S_8 and RNC, see: (a) Fujiwara, S.; Shin-Ike, T. *Tetrahedron Lett.* **1991**, *32*, 3503−3506. (b) Nishikawa, K.; Umezawa, T.; Garson, M. J.; Matsuda, F. *J. Nat. Prod.* **2012**, *75*, 2232−2235.

(13) Yonke, B. L.; Reeds, J. P.; Zavalij, P. Y.; Sita, L. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 12342−12346.

(14) Reeds, J. P.; Yonke, B. L.; Zavalij, P. Y.; Sita, L. R. *J. Am. Chem. Soc.* **2011**, *133*, 18602−18605.

(15) Yonke, B. L.; Reeds, J. P.; Fontaine, P. P.; Zavalij, P. Y.; Sita, L. R. *Organometallics* **2014**, *33*, 3239−3242.

(16) Farrell, W. S.; Zavalij, P. Y.; Sita, L. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 4269−4273.

(17) Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*, 1−24.

(18) Fontaine, P. P.; Yonke, B. L.; Zavalij, P. Y.; Sita, L. R. *J. Am. Chem. Soc.* **2010**, *132*, 12273−12285.

(19) Details are provided in the Supporting Information.

(20) (a) Pombeiro, A. J. L.; Chatt, J.; Richards, R. L. *J. Organomet. Chem.* **1980**, *190*, 297−304. (b) Morsing, T. J.; Bendix, J. *J. Mol. Struct.* **2013**, *1039*, 107−112.

DOI: 10.1021/acs.organomet.6b00302
Organometallics XXXX, XXX, XXX−XXX

(21) (a) Gambarotta, S.; Fiallo, M. L.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Inorg. Chem.* **1984**, *23*, 3532−3537. (b) Bianchini, C.; Masi, D.; Mealli, C.; Meli, A. *Inorg. Chem.* **1984**, *23*, 2838−2844. (c) Ohnishi, T.; Seino, H.; Hidai, M.; Mizobe, Y. *J. Organomet. Chem.* **2005**, *690*, 1140−1146. (d) Huang, N.; Li, X.; Xu, W.; Sun, H. *Inorg. Chim. Acta* **2013**, *394*, 446−451. (e) Merola, J. S.; Grieb, A. W. *Acta Cryst.* **2014**, *E70*, 352−354.

(22) Miessler, G. L.; Tarr, D. A. *Inorganic Chemistry*, 5th ed.; Prentice Hall: Englewood Cliffs, NJ, 2013.

(23) Stoichiometric SAT between a dinuclear disulfide and an isonitrile to produce an ITC has been reported; see: (a) Helton, M. E.; Maiti, D.; Zakharov, L. N.; Rheingold, A. L.; Porco, J. A., Jr.; Karlin, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1138−1141. (b) Maiti, D.; Woertink, J. S.; Vance, M. A.; Milligan, A. E.; Narducci Sarjeant, A. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2007**, *129*, 8882−8892.

(24) (a) Schwarz, D. E.; Rauchfuss, T. B. *Chem. Commun.* **2000**, 1123−1124. (b) Mallard, A.; Marrot, J.; Simonnet-Jégat, C.; Sécheresse, F. *Inorg. Chim. Acta* **2007**, *360*, 3436−3441. (c) Lee, S. G.; Choi, K. Y.; Kim, Y. J.; Park, S.; Lee, S. W. *Polyhedron* **2015**, *85*, 880−887.

(25) Dai, Q. X.; Seino, H.; Mizobe, Y. *Dalton Trans.* **2011**, *40*, 11822−11830.

(26) Kücükgüzel, S. G.; Kücükgüzel, I.; Tatar, E.; Rollas, S.; Sahin, F.; Güllüce, M.; De Clercq, E.; Kabasakal, L. *Eur. J. Med. Chem.* **2007**, *42*, 893−901.

(27) Schuster, R. E.; Scott, J. E.; Casanova, J. *Org. Synth.* **1966**, *46*, 75−77.

DOI: 10.1021/acs.organomet.6b00302
Organometallics XXXX, XXX, XXX−XXX