

Fe/Thiol Cooperative Hydrogen Atom Transfer Olefin Hydrogenation: Mechanistic Insights that Inform Enantioselective Catalysis

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ABSTRACT: Asymmetric hydrogenation of activated olefins using transition metal catalysis is a powerful tool for synthesis of complex molecules, but traditional metal catalysts have difficulty with enantioselective reduction of electron-neutral, electron-rich, and minimally functionalized olefins. Hydrogenation based on radical, metal-catalyzed hydrogen atom transfer (mHAT) mechanisms offers an outstanding opportunity to overcome these difficulties, enabling mild reduction of these challenging olefins with selectivity that is complementary to traditional hydrogenations with H₂. Further, mHAT presents an opportunity for asymmetric induction through cooperative hydrogen atom transfer (cHAT) using chiral thiols. Here, we report insights from mechanistic study of an iron-catalyzed achiral cHAT reaction and leverage these insights to deliver stereocontrol from chiral thiols. Kinetic analysis and variation of silane structure point to the transfer of hydride from silane to iron as the likely rate-limiting step. The data indicate that the selectivity-determining step is quenching of the alkyl radical by thiol, which becomes a more potent H-atom donor when coordinated to iron(II). The resulting iron(III)–thiolate complex is in equilibrium with other iron species, including Fe^{II}(acac)₂, which is shown to be the predominant off-cycle species. The enantiodetermining nature of the thiol trapping step enables enantioselective net hydrogenation of olefins through cHAT using a commercially available glucose-derived thiol catalyst, with up to 80:20 enantiomeric ratio. To the best of our knowledge, this is the first demonstration of asymmetric hydrogenation via iron-catalyzed mHAT. These findings advance our understanding of cooperative radical catalysis and act as a proof of principle for development of enantioselective iron-catalyzed mHAT reactions.

INTRODUCTION

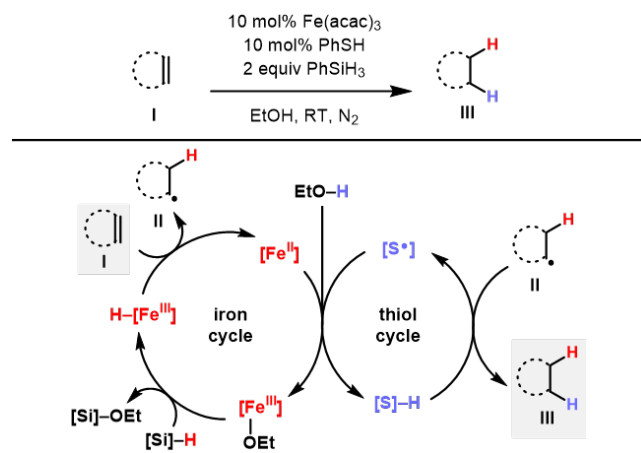
Historical Background. Asymmetric hydrogenation of olefins is among the most widely used transformations to prepare chiral molecules from prochiral substrates,¹ with classic methods for transition metal-catalyzed asymmetric hydrogenation based on the oxidative addition of H₂ (Scheme 1a).² While these reactions are highly efficient and widely used, they historically require substrates with coordinating functional groups for chelating, two-point metal binding to facilitate enantioinduction³ with limited exceptions.⁴ Further, the highest enantioselectivity is observed with electron-poor olefins (“activated olefins”), as interactions between the substrate and the metal are best promoted by substituents on the olefin that are typically electron-withdrawing.⁵ Recently, hydrogenation of electron-neutral, electron-rich (“unactivated”), and minimally functionalized olefins has seen growing improvement and success; however, lower enantioselectivity is commonly observed, and fewer methods are available.⁶

In this context, radical hydrofunctionalization enabled by metal-catalyzed hydrogen atom transfer (mHAT) reactions have particular promise as they do not require metal coordination of the olefin for reactivity.⁷ Mechanistically, mHAT involves a metal–hydride intermediate that transfers H• to the olefin to generate an alkyl radical that may be trapped under mild conditions. mHAT chemistry has been used for olefin hydrofunctionalizations⁸ with inexpensive Fe, Co, and Mn catalysts and exhibits excellent functional group tolerance, permitting late-stage functionalizations in total synthesis.⁹

In 2014, the Shenvi and Herzon groups independently published olefin hydrogenation by manganese- and cobalt-catalyzed mHAT respectively, trapping the transient alkyl radical with a second HAT step.^{8b, e, f, n} mHAT has some advantages over typical transition metal-catalyzed hydrogenations of olefins, which proceed by additions of H₂. First, unactivated olefins react well in mHAT methods, enabled by the high reactivity (low bond dissociation energy) of the weak metal–hydride bond.^{8b} The hydride source and reductant in mHAT is a silane or borohydride,^{8a, 8b, 8n, 10} enabling selective monoreduction of a polyalkene via stoichiometry control, which would be more challenging using a traditional hydrogenation in which the reductant is 1 atm of H₂ or solvent alcohol. Finally, the radical mechanism offers complementary selectivity relative to a typical transition-metal catalyzed mechanism, with improved chemoselectivity and preservation of sensitive functional groups.^{8a, 8b, 8n, 10}

One problem with these single-catalyst mHAT systems (Scheme 1b) is that they require at least stoichiometric loading of an oxidant, such as *tert*-butyl hydroperoxide (TBHP), which is necessary to turn over the M²⁺/M³⁺ cycle. While enabling, the inclusion of this oxidant reduces the atom economy of the reaction and can introduce some additional safety considerations.¹¹ In 2020, West and coworkers addressed this problem with the cooperative hydrogen atom transfer

**Scheme 2. Previously proposed mechanism for olefin hydro-
genation via iron and thiol cHAT**



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(cHAT) method for the chemoselective hydrogenation of unactivated olefins (Scheme 1c).¹² In cHAT, an Fe-based catalyst is complemented by a catalytic amount of a thiol that rapidly traps the alkyl radical to give the net hydrogenation product. The catalysts can be regenerated while avoiding the use of a stoichiometric oxidant. The cHAT system provides a facile method for olefin hydrogenation with up to 93% yield.

The original report of olefin hydrogenation by cHAT suggested a mechanism with two intersecting cycles (Scheme 2).¹² In the iron cycle (left/red intermediates), the iron(III) catalyst reacts with PhSiH₃ to generate the iron(III) hydride complex, which undergoes mHAT to the unactivated olefin **I** to generate the alkyl radical **II**. Then, a thiol HAT cycle (right/blue intermediates) provides the radical trap to generate hydrogenated product **III**. The thiyl radical then intercepts the iron(II) intermediate to regenerate the iron(III) and thiol. One striking feature of the system is the overall compatibility of intersecting cycles predicated on the mutual roles for Fe-based catalyst and thiols. A number of experiments supported this mechanistic model: TEMPO inhibition suggests the presence of radical intermediates; deuterium labeling studies support that the EtOH/thiol exchange is the source of the second H•, which is delivered to the alkyl radical through the thiol catalytic cycle. However, important mechanistic questions remained, particularly about the intersection of the two cycles. For example, how does the system avoid the plausible inhibition of the iron catalyst by thiol/thiolate donors? What is the speciation of the iron catalyst? Is the radical trap the free thiol or an Fe–thiol complex? Additionally, can chiral information be introduced via the thiol to influence the stereochemistry of the second C–H bond forming event? These questions were the motivating force behind the study described herein.

Asymmetric Hydrogen Atom Transfer Reactions. Several recent advances have been made in the development of methods for enantioselective mHAT olefin hydrofunctionalization, each of which uses cobalt catalysts with chiral ligands. These examples include both intramolecular and intermolecular reactions with alcohols,¹³ heteroarenes,¹⁴ and various nitrogen sources.¹⁵ To the best of our knowledge, however, no studies have reported any enantioselective mHAT olefin functionalization or hydrogenation that uses an

Fe-based catalyst. This difference between metals may be due to the higher bond dissociation free energy (BDFE) of the Co–C bond in the cobalt(IV)–alkyl intermediate (calcd. 22 kcal/mol¹⁶) relative to the very weak BDFE for the putative Fe–C bond in the iron(III)–alkyl intermediate (calcd. 1.5 kcal/mol¹⁷). Indeed, organocobalt species arising from cobalt mHAT can be isolated,^{16,18} while analogous alkyl intermediates from iron mHAT have yet to be characterized experimentally. The relative stability of [Co^{IV}]–alkyl intermediates in particular enables them to undergo nucleophilic attack via an S_N2 mechanism and to provide enantioinduction through use of a chiral ligand.^{8b,15b,16,18–19} In contrast, the Fe–C bond is too weak to proceed through a similar S_N2 mechanism, homolyzing before any opportunity arises for chiral information to be transmitted by a supporting ligand.

The presence of the thiol/thiyl catalytic cycle in cHAT olefin hydrogenation provides a unique opportunity to circumvent this challenge through use of a chiral thiol co-catalyst, introducing stereochemistry during the alkyl radical trapping/C–H bond-forming step. We note that thiols have been used as chiral HAT catalysts to provide stereocontrol through asymmetric delivery of H• to alkyl radicals. In early studies, Roberts pioneered the use of chiral thioglycosides as HAT catalysts to provide enantioinduction in olefin hydrosilylation.²⁰ Recently, the Ye group developed methods with both chiral thioglycosides and cysteine-based peptide catalysts for asymmetric olefin functionalization.²¹ In additional applications of cysteine-based peptide catalysts as chiral HAT catalysts, the Miller and Knowles groups reported enantioselective HAT in the deracemization of cyclic ureas²² and the hydroamination of olefins.²³

From these examples and our working understanding of cHAT, we hypothesized that a chiral thiol catalyst could be used to confer asymmetry in Fe and thiol cHAT olefin hydrogenation. Here, we demonstrate the plausibility of these ideas, starting with kinetic analysis, spectroscopy, and computations that enable better understanding of the symbiotic operation of the two cycles in Scheme 2. Using this mechanistic insight, we then show that chiral thiol catalysts can indeed lead to significant stereocontrol in olefin hydrogenation. With selectivities of up to 80:20 er, though modest, this work provides the first demonstrations of asymmetric induction in iron-catalyzed mHAT reactions. These results show the promise for further development of enantioselective catalysts with mHAT and provide firm mechanistic footing for such studies.

RESULTS AND DISCUSSION

Initial Kinetic Analysis Using PhSiH₃. The reaction orders in the observed rate law for the achiral cHAT olefin hydrogenation reaction (Figure 1) were evaluated by monitoring product formation using GC. We used two complementary methods to increase our confidence about the conclusions. The first was to assess the entire reaction course graphically with variable time normalization analysis (VTNA).²⁴ The second was to use initial rate measurements. Employing each kinetic technique, the order of the rate dependence on PhSiH₃ can be reasonably fit to either +0.5 or +1 order in [PhSiH₃], with a clear positive rate dependence (Figure 1 for VTNA, see SI for initial rate data). The rate dependences on [olefin] and [thiol] were found to be zero order (see SI for detailed analysis).

Surprisingly, the best fits for the rate (using VTNA or initial rates) indicated a pseudo-zero order dependence on $[\text{Fe}]$. Using VTNA, there is a deviation at later time points, prompting us to test for catalyst deactivation using a method derived from reaction progress kinetic analysis.²⁵ Two hydrogenation reactions were conducted in parallel, with the first unchanged from standard conditions. The second reaction started with lower concentration of starting material but included the independently prepared product to mimic a partially complete reaction, but without any catalyst deactivation.

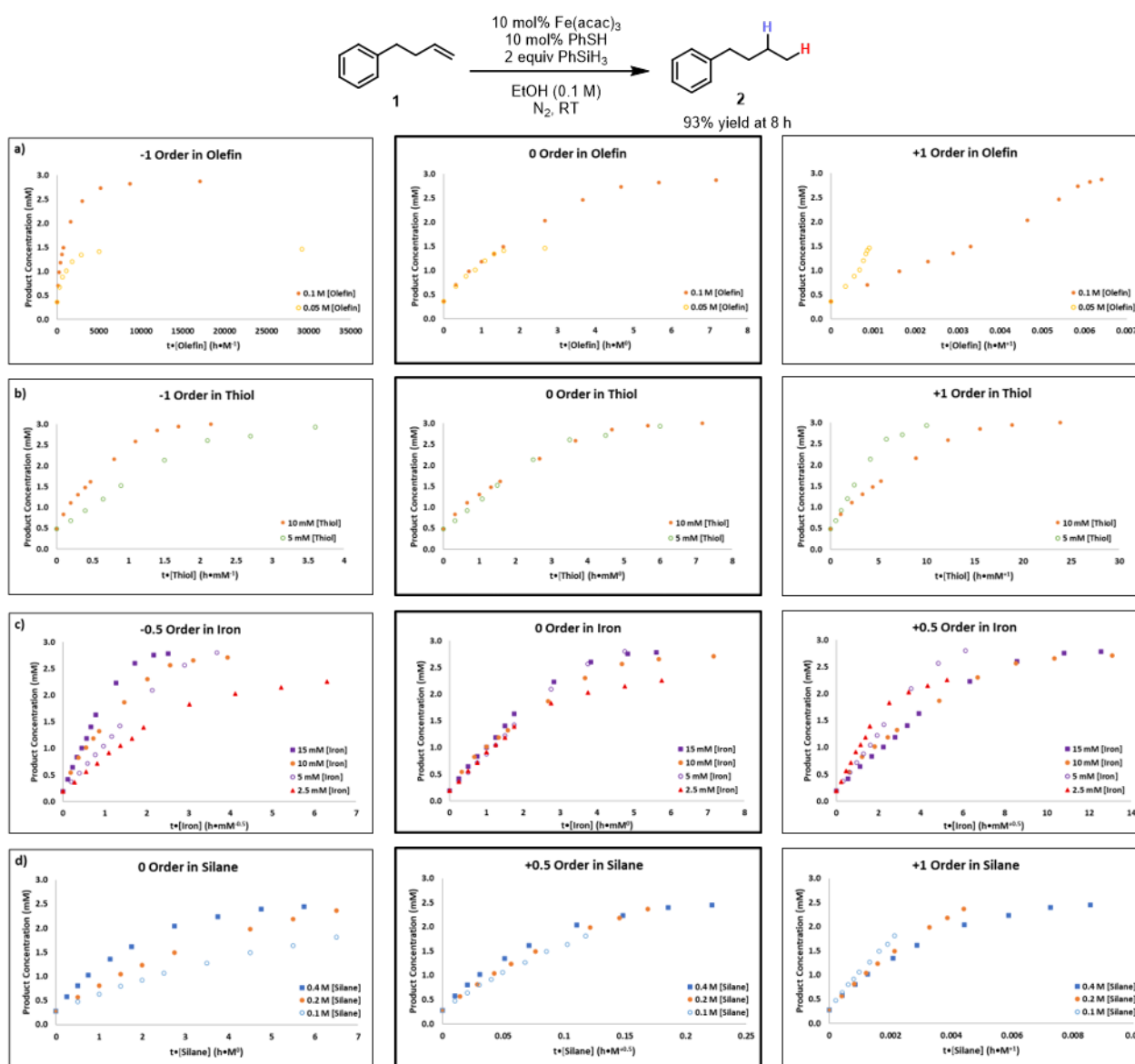


Figure 1. VTNA of PhSiH_3 kinetics data fitting different rate orders for a) olefin, b) thiol, c) iron, and d) silane.

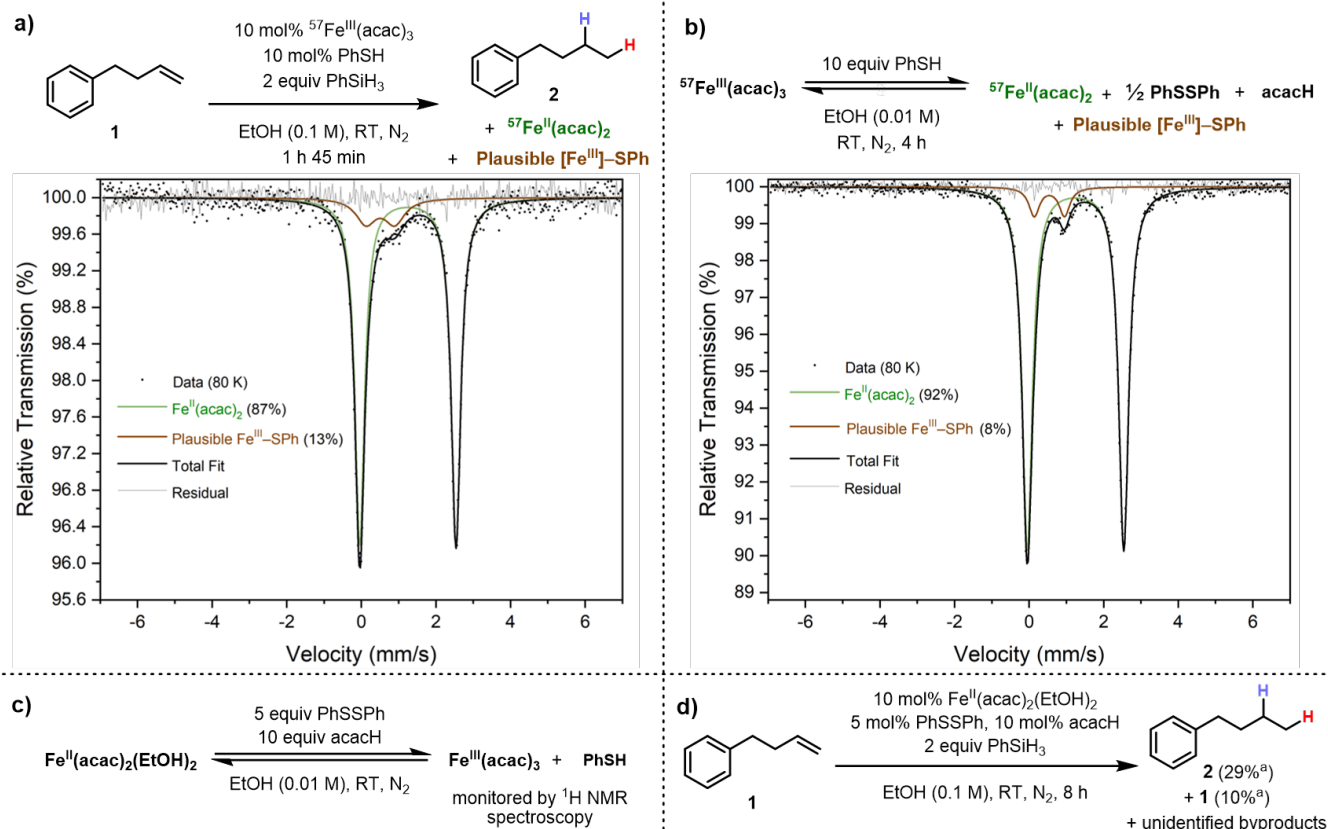


Figure 2. a) Olefin hydrogenation reaction monitored by freeze-trapped solution-state Mössbauer spectroscopy. The spectrum has been fit to the following parameters for $\text{Fe}^{\text{II}}(\text{acac})_2$ — $\delta = 1.25$ mm/s, $|\Delta E_Q| = 2.58$ mm/s, $\Gamma = 0.31$ mm/s and for the plausible $[\text{Fe}^{\text{III}}]\text{-SPh}$ complex — $\delta = 0.51$ mm/s, $|\Delta E_Q| = 0.77$ mm/s, $\Gamma = 0.65$ mm/s. b) Reduction of iron(III) to iron(II) by PhSH, monitored by freeze-trapped solution-state Mössbauer spectroscopy. The spectrum has been fit to the following parameters for $\text{Fe}^{\text{II}}(\text{acac})_2$ — $\delta = 1.24$ mm/s, $|\Delta E_Q| = 2.58$ mm/s, $\Gamma = 0.33$ mm/s and for the plausible $[\text{Fe}^{\text{III}}]\text{-SPh}$ complex — $\delta = 0.54$ mm/s, $|\Delta E_Q| = 0.81$ mm/s, $\Gamma = 0.34$ mm/s. c) Oxidation of iron(II) to iron(III). d) Olefin hydrogenation reaction with iron(II) and PhSSPh. ^aPercent yield determined by ^1H NMR with 1,4-bis(trimethylsilyl)benzene as internal standard.

Importantly, the two reaction profiles *do not* overlay (see SI), suggesting that catalyst deactivation occurs during catalysis. This result could help explain the pseudo-zero rate order in catalyst and is addressed in more detail below ("Identifying the Catalyst Deactivation Pathway"). Perhaps the most salient conclusion from the kinetics, however, is that while the rate is independent of olefin and thiol concentrations, it is dependent on [silane], suggesting that silane is part of the turnover-limiting step. This finding is consistent with mechanistic studies on iron-catalyzed mHAT olefin-olefin cross-coupling, which shares several common intermediates.^{8b, 17} The slowest step in the coupling reaction is formation of the $[\text{Fe}^{\text{III}}]\text{-H}$ intermediate, which is high-energy and requires overcoming a high-energy transition state for its formation. This seems to be the case for the cHAT hydrogenation studied here as well.

Kinetics Using $\text{PhSi}(\text{O}i\text{Pr})\text{H}_2$. To further investigate the role of silane in determining the rate, we tested $\text{PhSi}(\text{O}i\text{Pr})\text{H}_2$, which was previously reported by Shenvi and coworkers to be highly active in mHAT reactions.²⁶ We found that replacing PhSiH_3 with $\text{PhSi}(\text{O}i\text{Pr})\text{H}_2$ significantly increases the rate of cHAT olefin hydrogenation, achieving the same >90% yield in 15 minutes rather than 8 hours. This finding supports the hypothesis that silane is involved in the turnover-limiting step of the catalytic reaction.

Since the reaction is performed in ethanol, we also assessed whether solvolysis of $\text{PhSi}(\text{O}i\text{Pr})\text{H}_2$ to $\text{PhSi}(\text{OEt})\text{H}_2$ occurs under the reaction conditions. First, we monitored a solution of 0.2 M

$\text{PhSi}(\text{O}i\text{Pr})\text{H}_2$ in EtOH by GC, which showed that formation of $\text{PhSi}(\text{OEt})\text{H}_2$ was already 91% complete within 2 min and is fully complete within 17 min. We also found that the catalytic hydrogenation was more rapid in ethanol than isopropanol (see details in SI). This indicates that the solvolysis of the silane is rapid under catalytic conditions, which is consistent with a lack of significant induction period. Efforts to establish the rate law with the alkoxyasilanes were unsuccessful (see SI), perhaps due to confounding kinetic contributions from solvolysis. We tentatively attribute the non-integer rate order for silane to silane decomposition via the known iron(II)-catalyzed solvolysis to form inactive silyl products, such as $\text{PhSi}(\text{OEt})_2\text{H}$ and $\text{PhSi}(\text{OEt})_3$.^{8b, 17}

To our knowledge, others have not considered this explanation for solvent dependence of mHAT rates.^{8b, 26} This implies that, in the future, other mHAT reactions could also be facilitated by using smaller alcohols as solvents because of decreased steric hindrance in transferring hydride from silane to the transition metal during the turnover-limiting step. Of course, the generality of this effect will need to be assessed in each reaction system separately.

Testing an Alternative Explanation – Silane Pre-Activation. We also considered that rate-limiting silane pre-activation through reaction with EtOH could explain the presence of only silane and not iron in the rate law of the PhSiH_3 system. Specifically, formation of the more active alkoxyasilane species, $\text{PhSi}(\text{OEt})\text{H}_2$, from PhSiH_3 could be catalyzed by ethoxide from solvent autoionization or by

EtOH directly. However, we were able to rule out this hypothesis by monitoring a solution of PhSiH₃ in EtOD by ¹H NMR spectroscopy over 10 h, during which we observed no detectable formation of new compounds. Therefore, uncatalyzed reaction of silane with solvent is an unlikely rate determining step.

Identifying the Catalyst Deactivation Pathway. In order to assess the nature of catalyst deactivation as identified in the kinetics, we examined the iron speciation during the catalytic reaction via ⁵⁷Fe Mössbauer spectroscopy. Solutions flash-frozen during catalysis (at approximately 45% conversion) using ⁵⁷Fe^{III}(acac)₃ showed that the majority of iron in the reaction was present as Fe^{II}(acac)₂ (Figure 2a). We considered that iron reduction could arise from homolysis of iron(III)–hydride and/or iron(III)–alkyl bonds,^{8b, 8h, 17} or from reduction by thiol. Examples from the literature abound for reduction of iron(III) by thiols,²⁷ and we sought to understand whether thiol plays a role in the formation of Fe^{II}(acac)₂ in cHAT olefin hydrogenation. Therefore, we treated Fe^{III}(acac)₃ with 10 equiv PhSH, which resulted in rapid, complete consumption of Fe^{III}(acac)₃ with formation of Fe^{II}(acac)₂ and PhSSPh, as identified by Mössbauer and ¹H NMR spectroscopies (Figure 2b). This deactivation path is further supported by the observed suppression of hydrogenation reactivity when running the reaction with excess thiol (see SI). Thus, the added thiol is a feasible culprit that leads to the inactive Fe^{II}(acac)₂ observed in the hydrogenation reaction. With only 1 equiv PhSH to 1 equiv Fe^{III}(acac)₃, however, only partial deactivation of Fe^{III}(acac)₃ to Fe^{II}(acac)₂ was observed by ¹H NMR spectroscopy (see SI). This is a plausible explanation for why the reaction is not completely suppressed under catalytic conditions.

Interestingly, this reduction of iron(III) by thiol is reversible. We found that the reaction of Fe^{II}(acac)₂(EtOH)₂, PhSSPh, and acetylacetone (acacH) produced Fe^{III}(acac)₃ as observed by ¹H NMR spectroscopy (Figure 2c). However, the efficiency of the iron oxidation pathway is impacted by the low solubility of Fe^{II}(acac)₂ in EtOH. To further probe the iron oxidation pathway, we tested the olefin hydrogenation reaction using 10 mol% Fe^{II}(acac)₂(EtOH)₂, 5 mol% PhSSPh, and 10 mol% acacH (Figure 2d). After 8 h, we observed 29% yield of hydrogenated product with incomplete consumption of olefin starting material. The observation of very sluggish catalysis indicates that the catalyst may be rescued, but this is not kinetically competent on the timescale of the catalytic reaction. Thus, we propose that the reason for the apparent zero-order rate dependence on [Fe] is that most of the iron in the reaction becomes

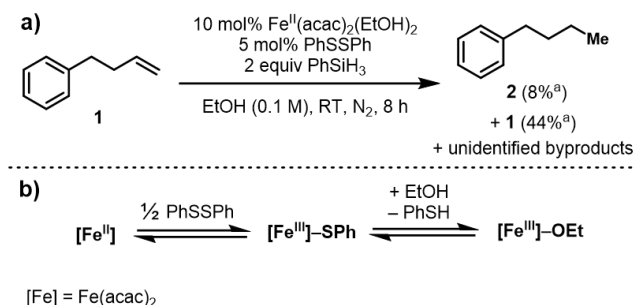
reduced and inactive. A small amount of catalyst (independent of the amount of added iron, since it is limited by the solubility of Fe^{II}(acac)₂) is participating in the catalytic reaction.

Plausible [Fe^{III}]-Thiolate Complex. During these efforts to identify catalyst deactivation, we also observed an unknown iron(III) species, which accounted for ~10% of the iron in the Mössbauer spectra of both the olefin hydrogenation and the iron reduction reaction (Figures 2a and 2b). As the parameters for this species were not consistent with those previously reported for an iron(III)–ethoxide complex ([Fe^{III}(acac)₂(μ-OEt)]₂, δ = 0.54 mm/s, |ΔE_Q| = 0.51 mm/s),¹⁷ we hypothesized that this unknown iron species could be an iron(III)–thiolate complex. As noted at the outset, the plausible interaction of the Fe-based catalysts with the thiol/thiyl catalyst represents one of the most intriguing aspects of thiol cHAT. Attempts to isolate and crystallize the iron(III) complex were unsuccessful. Therefore, we turned to density-functional theory (DFT) calculations to compute Mössbauer parameters for plausible iron(III)–thiolate complexes, for comparison to Mössbauer spectra of the mixtures generated *in situ*. We found that the calculated Mössbauer parameters for several possible iron(III)–thiolate complexes, including monomers and bridging diiron complexes, are consistent with the experimental values of the unknown complex (see SI). The broadness of the peak observed in Figure 2a suggests that it is not a single thiolate species; it may be a mixture of complexes with differing nuclearities. Though the precise structure is not clear from these spectroscopic measurements, these studies support the feasibility of iron–thiolate species.

The iron(III)–thiolate complex may be an intermediate of the iron reduction and/or an intermediate of the catalytic cycle. To probe the latter proposal, we tested the hydrogenation reaction with 10 mol% Fe^{II}(acac)₂(EtOH)₂ and 5 mol% PhSSPh in the absence of acacH (Scheme 3a). After 8 h, we observed 8% product formation and incomplete consumption of starting material. In the absence of acacH, the formation of product may proceed through the [Fe^{III}]-SPh intermediate (Scheme 3b). Our results are consistent with [Fe^{III}]-SPh being on-cycle or in equilibrium with an on-cycle species.

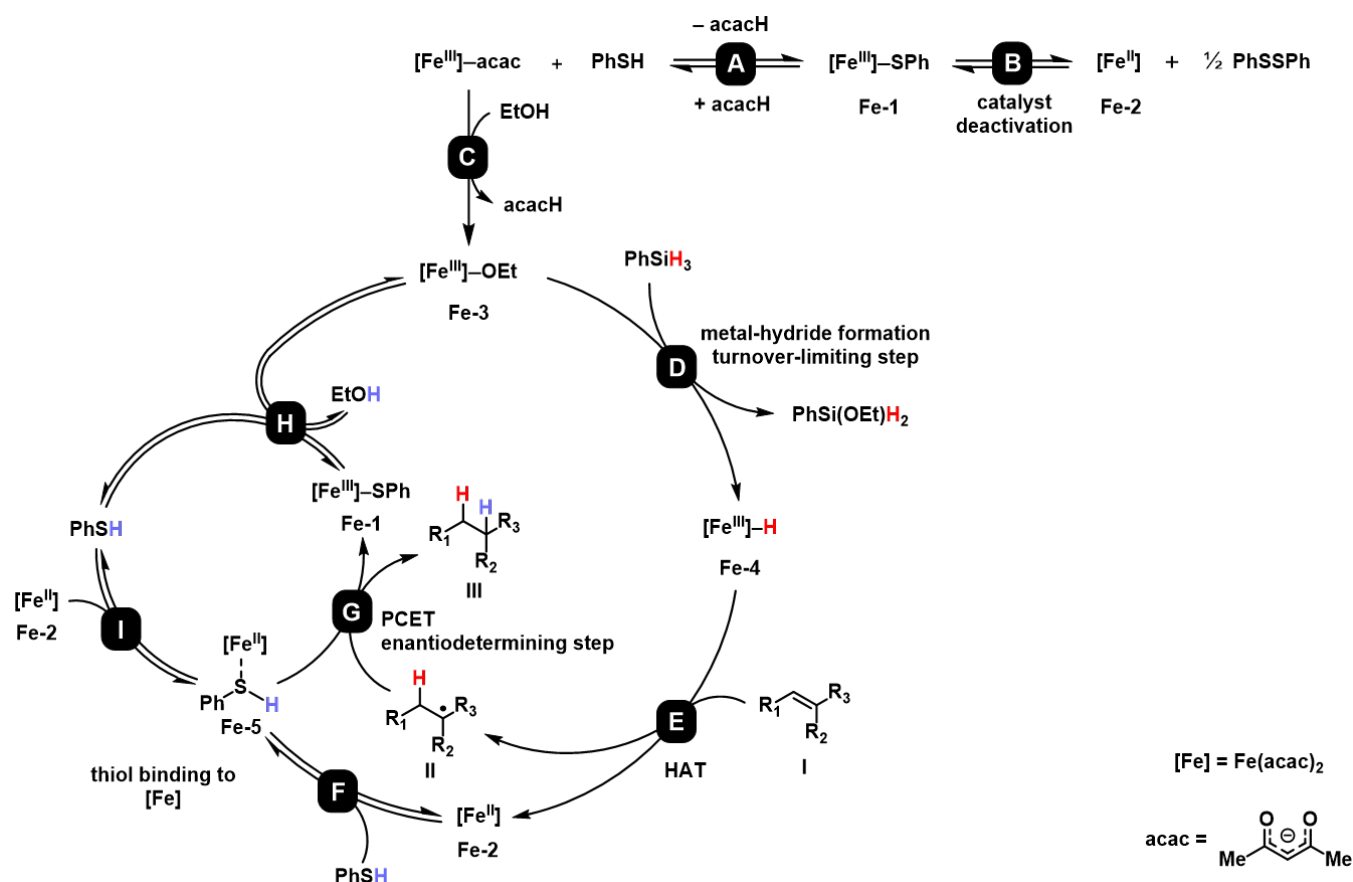
Thiol Binding to Iron(II). In the iron-catalyzed olefin-olefin cross-coupling via HAT, we proposed that the alkyl radical generated following HAT is quenched via proton-coupled electron transfer (PCET) from an iron(II) ethanol complex, a step which is enabled by the lowering of the O–H BDFE upon coordination of EtOH to the iron center.¹⁷ The cHAT olefin hydrogenation system presents an opportunity to form an analogous iron(II) thiol complex, which would likewise have a decreased S–H BDFE. The feasibility of an iron(II)–thiol interaction is supported by literature suggesting

Scheme 3. a) Olefin hydrogenation reaction with iron(II) and PhSSPh in the absence of acacH; b) Proposed pathway for [Fe^{III}]-SPh in equilibrium with on-cycle species, [Fe^{III}]-OEt



^aPercent yield determined by ¹H NMR with 1,4-bis(trimethylsilyl)benzene as internal standard.

Scheme 4. Proposed catalytic cycle for olefin hydrogenation by iron and thiol cHAT^a



^aProposed neutral ligands, such as EtOH, have been omitted for clarity. Step F and Step I are identical but are shown twice for clarity.

that cysteine binds as a neutral donor to iron(II) heme complexes.²⁸ While Lewis basic ligands with oxygen, nitrogen, and phosphorus donor atoms are known to coordinate to Fe^{II}(acac)₂, to the best of our knowledge no studies have yet reported evidence for binding of neutral sulfur-based ligands.²⁹ Therefore, we sought to experimentally probe whether thiol binds to iron(II) under conditions relevant to olefin hydrogenation.

We began by monitoring a mixture of Fe^{II}(acac)₂(EtOH)₂ and 10 equiv PhSH in ethanol-*d*₆ by ¹H NMR spectroscopy. We observed no evidence of thiol binding, potentially due to competition with EtOH. Accordingly, we monitored the reaction in 95:5 toluene-*d*₈: ethanol-*d*₆. At low temperatures, we observed peak broadening and a shoulder peak by ¹H NMR spectroscopy, indicating a change in speciation of Fe^{II}(acac)₂(EtOH)₂. Though the broad peaks do not enable us to elucidate the structure, this observation is consistent with weak PhSH binding to iron(II), which leads to an equilibrium mixture containing some amount of thiol complex.

Using DFT calculations (B3LYP/ZORA-def2-TZVP), we calculated the binding energy of the thiol in the hypothetical molecule Fe^{II}(acac)₂(EtOH)(PhSH) to be 19 kcal/mol. To further investigate the effects of thiol coordination to iron(II), we calculated the BDFE of the S–H bond in this iron(II) complex. Upon binding to Fe^{II}(acac)₂(EtOH), the BDFE of the S–H bond in PhSH is predicted to weaken from 82 to 66 kcal/mol (see SI for additional BDFE calculations). Therefore, binding to iron(II) would make the S–H bond weaker than the O–H bond in iron(II) ethanol complexes (calcd. 70 kcal/mol), and it could react rapidly with the alkyl radical.

Indeed, attempts to locate a transition state along the pathway of hydrogen atom transfer showed that the reaction is practically barrierless. Thus, all of our evidence suggests that an iron(II)-thiol complex can quench the alkyl radical extremely rapidly.

Proposed Catalytic Cycle. Based on the above experiments and analysis, a catalytic cycle for olefin hydrogenation by iron and thiol cHAT is proposed in Scheme 4. In a catalyst deactivation pathway, Fe^{III}(acac)₃ reacts with PhSH to form Fe^{II}(acac)₂ (**Fe-2**) and PhSSPh, proceeding through the iron(III)-thiolate intermediate **Fe-1** (Steps A and B). This process is reversible; however, the poor solubility of Fe^{II}(acac)₂ limits the rate of oxidation of iron to re-enter the cycle.

We propose that the low concentration of Fe^{III}(acac)₃ forms the active iron(III)-ethoxide catalyst **Fe-3** (Step C), which reacts with PhSiH₃ in the turnover-limiting step to form iron-hydride **Fe-4** (Step D). Following HAT to the olefin **I**, an alkyl radical **II** is generated (Step E). PhSH then coordinates to the resulting iron(II) intermediate **Fe-2** to form an iron(II) thiol complex **Fe-5** (Step F). While we cannot rule out that alkyl radical **II** is quenched by free thiol, we propose that **II** is primarily quenched via PCET from **Fe-5**, due to the lowered S–H BDFE upon binding to iron. This generates the hydrogenated product **III** and the iron(III)-thiolate complex **Fe-1** (Step G). Finally, **Fe-1** undergoes ligand exchange to regenerate PhSH and **Fe-3**. This mechanism is supported by observation of Fe^{II}(acac)₂ and a likely iron(III)-thiolate species by Mössbauer spectroscopy, as well as the stoichiometric reactions shown in Figure 2.

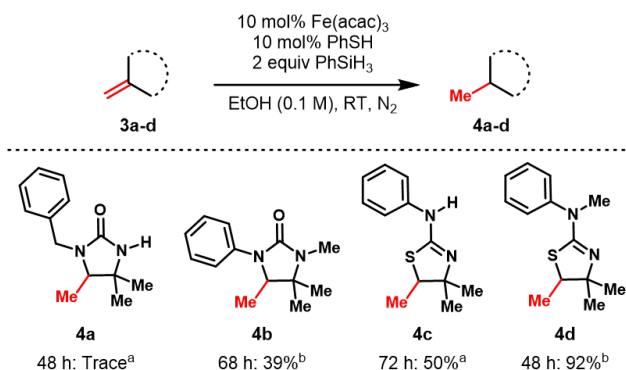
Evaluating the Potential for Enantioinduction. In the catalytic cycle shown in Scheme 4, a stereogenic center is set when radical **II** reacts with a formal H-atom donor. Accordingly, we envisioned that use of a chiral thiol may allow Step **G** to serve as an enantiodetermining step. To assess the possibility of enantioselective catalysis, we designed a small set of prochiral substrates. We took inspiration from multiple sources, opting for a heterocyclic substrate with exocyclic olefin modeled after the lactone substrates utilized by Roberts and coworkers.^{20a, 30} The exocyclic olefins that lead to the products shown in Scheme 5 also would proceed through intermediate radicals that would bear structural homology to the alkyl radical intermediate accessed in recent work of Miller, Knowles, and coworkers, in which enantioselective HAT from a thiol was integral to substrate deracemization.²² With synthetic accessibility in mind, we thus prepared the *N*-aryl cyclic ureas and *N*-aryl thiazolidines **3a–d**. Of note, thiazolidines are biologically-active structural scaffolds with various documented applications.³¹

Intriguingly, we found minimal to low conversion with the cyclic ureas **3a–b**, potentially arising from inhibition through coordination with the iron catalyst. However, the thiazolidines were well tolerated, affording higher conversion to product. In particular, the methylated thiazolidine **3d** reached 92% conversion to product **4d** within 48 hours and was therefore prioritized for further study.

We performed preliminary optimization of the achiral method with the model substrate **3d**, beginning with assessment of the metal catalyst. We screened several commercially available metal catalysts with established reactivity in mHAT transformations (Table 1, entries 1–3).^{8e, 8f, 32} Ultimately, we found that other catalysts did not perform better than Fe(acac)₃, in agreement with the original report of the cHAT system (Table 1, entry 1).¹² We found that a slightly higher loading of 15 mol% metal catalyst (Table 1 entry 4) afforded higher conversion to product. Higher concentration (Table 1 entry 5) had minimal impact on conversion, so we moved forward with conditions as in entry 4. Additional screening results are detailed in the SI.

With the development of a high yielding reaction mediated by fully achiral components, we began to test the feasibility of asymmetric hydrogenation with a commercially available chiral thiol: a

Scheme 5. Screen of prochiral substrates under original conditions



^aPercent conversion determined by ¹H NMR as the crude ratio of starting material to product peaks. ^bPercent conversion determined by GC-FID as the crude ratio of starting material to product peaks.

Table 1. Initial optimization of metal catalyst

Entry	Time (h)	Metal Catalyst	Loading (mol%)	Conversion to Product (%) ^a
1	24	Fe(acac) ₃	10	93
2	41	Co(salen)	10	35
3	41	Mn(dpm) ₃	10	7
4	24	Fe(acac) ₃	15	98
5 ^b	24	Fe(acac) ₃	15	97

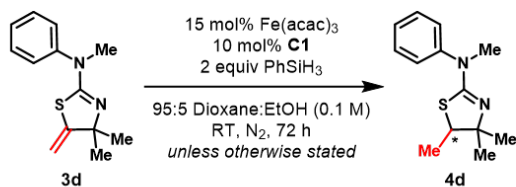
^aPercent conversion determined by GC-FID as the crude ratio of starting material to product peaks. ^bReaction concentration 0.2 M.

thioglycoside utilized by Roberts and coworkers (**C1**).^{20a, 30} The current conditions (Table 2, entry 1) afforded a high yield but minimal enantioinduction. A number of variations led to alteration of the reaction efficiency but no enhanced enantioselectivity. For example, moderate heating to 50 °C led to lower yield and nearly racemic

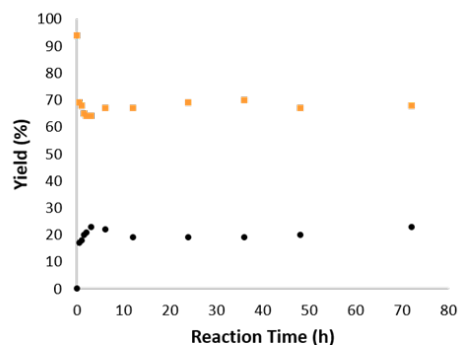
Table 2. Solvent screen for enantioselectivity

Entry	Solvent	Conversion to Product (%) ^a	er ^b
1	EtOH	91	52:48
2 ^c	EtOH	57	53:47
3	iPrOH	58	53:47
4	95:5 THF:EtOH	37	59:41
5	95:5 Benzene:EtOH	51	57:43
6	95:5 Dioxane:EtOH	37	61:39
7 ^d	95:5 Dioxane:iPrOH	10	55:5:44:5

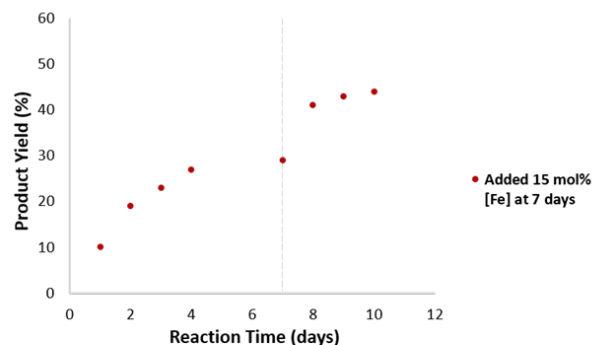
nd = not determined. ^aPercent conversion determined by GC-FID as the crude ratio of starting material to product peaks. ^bEnantiomeric ratio (er) determined by HPLC with a chiral stationary phase. Peaks reported in order of elution. ^cReaction temperature 50 °C. ^dReaction time 72 h.



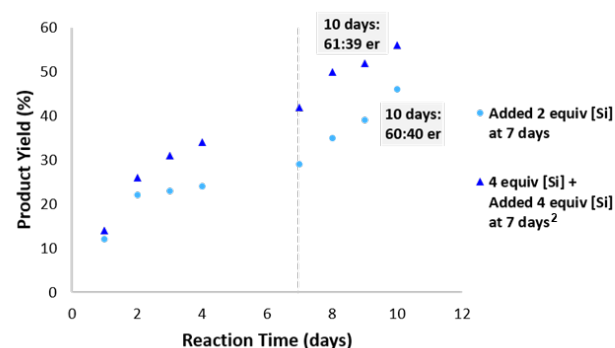
a) Reaction profile¹



b) Iron spiking



c) Silane spiking



d) Iron and silane spiking

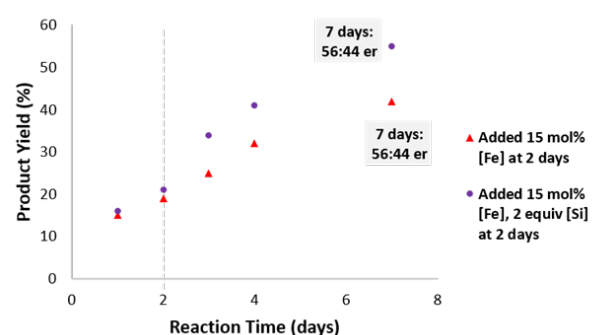


Figure 3. Reaction profile and spiking of iron and silane. Percent yield determined by GC-FID with a calibration curve. ¹Reaction run with 7.5 mol% $[\text{Fe}^{\text{III}}(\text{acac})_2(\mu\text{-OEt})_2]$. ²Reaction was initially set up with 4 equiv PhSiH_3 . An additional 4 equiv PhSiH_3 was added at 7 days.

product (Table 2, entry 2). Changing the EtOH solvent to *i*PrOH similarly decreased reaction efficiency (Table 2, entry 3).

We hypothesized that pure alcohol solvents may disrupt noncovalent interactions between substrate and thiol catalysts, prompting us to explore solvent mixtures that contained nonpolar co-solvents (Table 2, entries 4–7). These changes enabled us to observe unambiguous enantioinduction for the first time (61:39 er), with the highest er obtained in 95:5 dioxane:EtOH mixture (Table 2, entry 6). Additional screening is presented in the SI.

Mechanistic Insights Into the Asymmetric Reaction. Mechanism-driven experiments allowed us to improve the yield of olefin hydrogenation to 74% yield in 24 h (improved from the original 26% yield in 72 h), while the er of 61:39 was retained. These studies are presented in Figure 3.

Figure 3a shows the reaction progress versus time for the reaction conditions listed in the equation. Notably, the majority of the conversion took place in the first 12–24 hours, at which point the reaction rate decreased. The loss of mass balance over time is minimal and consistent throughout the reaction. This behavior is characteristic of catalyst deactivation, as described above from mechanistic studies of the achiral reaction. We additionally monitored er over time, and found that the enantioselectivity was consistent over the course of the reaction (see SI). In the remainder of the studies, mass

balance remains satisfactory, so we focus our attention on product formation and er only.

We next sought to investigate iron, silane, and thiol as possible sources of the deactivation when employing a chiral thiol catalyst. We began by spiking the reaction with additional iron catalyst (Figure 3b) to test if the reaction would reinitiate after deactivation. We allowed the initial reaction to proceed for 7 days to ensure complete rate drop off, then added an extra 15 mol% of solid $\text{Fe}(\text{acac})_3$ (indicated by the light gray line on Figure 3b) and monitored the reaction further. The reaction rate increased after the iron spiking, giving increased overall yield. However, this rate increase is short lived and once again dwindles, further supporting iron deactivation as a main source of the decreasing rate.

Next, we added additional silane during the catalytic reaction, through two separate experiments as defined in Figure 3c. Each addition led to increases in reaction rate and yield, implying that silane decomposition is also occurring. We further observed no reduction of er.

We then repeated the iron spiking on a shorter timescale adding 15 mol% $\text{Fe}(\text{acac})_3$ at two days and observed lower er (Figure 3d). Finally, we found the observed effects on yield and er were additive when both iron and silane were spiked together. Our individual spiking observations hold true in the combined case; enantioinduction

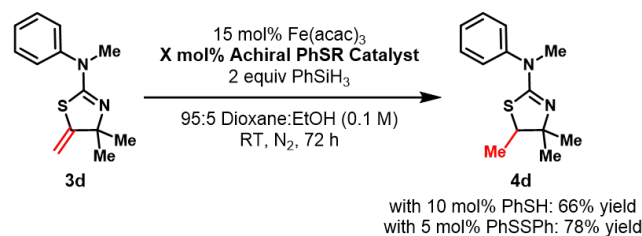
is not impacted by extra silane, but is reduced in the presence of extra iron, regardless of whether extra silane is added simultaneously.

We hypothesize that higher concentrations of iron may increase the rate of the racemic background iron-only reactivity excluding thiol, in analogy to Shenvi and Herzon's hydrogenation systems,^{8e,f} resulting in the observed degradation of *er*. Overall, the various spiking studies support the possibility of catalyst deactivation arising from both iron and silane, a result consistent with the kinetic results above. However, the yield increase from spiking is only moderate even when carried out for both iron catalyst and silane. Additional spiking and loading studies are available in the SI.

Additionally, since disulfide is present under catalytic conditions as a result of catalyst deactivation (see above), we chose to test the competency of disulfides themselves as catalysts or precatalysts. Employing achiral disulfides, we found comparable yields between PhSH and PhSSPh (Scheme 6, see SI for other tests). Given that the reaction is generally under reductive conditions, it is plausible that any disulfides (pre-formed or made *in situ*) can be reduced to their active free thiol in solution. Therefore, we conclude the formation of disulfides in the catalytic reaction is not a major source of catalyst deactivation or sequestration.

Modulation of Enantioselectivity. We then turned our attention to screening a variety of chiral thiols derived from both peptides and carbohydrates to supplement our initial examination of **C1** (Table 3, entry 1). With peptide-derived catalysts, the thiol source was primarily derived from incorporation of cysteine (Table 3, entries 2-4). Unfortunately, these cysteine catalysts provided minimal enantioinduction. Based on our previous finding that achiral disulfides

Scheme 6. Testing disulfide in the reaction^a



^a Percent yield determined by GC-FID with a calibration curve.

were competent precatalysts, we compared a corresponding chiral disulfide/free thiol pair (Table 3, entries 4-5). Chiral disulfide **C5** does generate product, a finding which agrees with our mechanistic work utilizing disulfides in the racemic system, but with reduced yields and minimal enantioinduction. We also tested a peptide containing an aromatic thiol (**C6**) rather than a cysteine, given its increased similarity to PhSH; however, it did not furnish appreciable enantioinduction (Table 3, entry 6). Additional screening of other peptide catalysts and chiral ligands is available in the SI.

Based on our early observation of enantioselectivity with **C1**, we wondered if alternate carbohydrate thiol catalysts would provide enhancement in *er* (Table 3, entries 7-9). We synthesized **C7** with the hypothesis that utilizing a bulkier protecting group on the sugar backbone may lead to increased enantioinduction; however, we observed no change in *er* (Table 3, entry 7). Utilizing a galactose backbone (**C8**) instead resulted in a minor erosion of *er* (Table 3, entry 8). Finally, the structurally dissimilar furanose catalyst **C9** provided slightly increased enantioinduction, but with a reversal of observed selectivity (Table 3, entry 9). Given the similarity of the results, we

continued with **C1** for method development based on its commercial availability and ease of handling.

Guided by the mechanistic insights described above, we performed additional screening of the asymmetric system in reference to the previous best result (Table 4, entry 1). First, we tested whether a more sterically demanding ligand could prevent catalyst deactivation by slowing down steps **A** and **B** of Scheme 4. Ligands were selected based upon previous reports by Baran and coworkers.³³ Similar to Baran's observations, we observed a balance between steric demands and reactivity. While both Fe(dpm)₃ and Fe(dibm)₃

Table 3. Testing chiral thiols

Entry	Chiral Thiol	Yield (%) ^a	<i>er</i> ^b
1	C1	26	61:39
2	Boc-Cys-OMe (C2)	48	51:49
3 ^c	Boc-Cys- ^D Pro-Acpc-Phg-NMe ₂ (C3)	16	49:51
4	Boc-Cys- ^D Pro-Aib-Phe-Pip (C4)	45	47:53
5	[Boc-Cys- ^D Pro-Aib-Phe-Pip] ₂ (C5)	12	49:51
6 ^d	2-thio-Bz- ^D Pro-Acpc-Cha-NMe ₂ (C6)	51	48:52
7	C7	31	61:39
8	C8	29	58:42
9	C9	35	37:63

Acpc = 1-aminocyclopropane-1-carboxylic acid, Aib = 2-aminoisobutyric acid, Cha = cyclohexylalanine, Phg = phenylglycine, Pip = piperidine. ^aPercent yield determined by GC-FID with a calibration curve. ^bEnantiomeric ratio (*er*) determined by HPLC with a chiral stationary phase. Peaks reported in order of elution. ^cReaction was run with 7.5 mol% [Fe^{III}(acac)₂(μ-OEt)]₂. ^dPercent conversion determined by GC-FID as the crude ratio of starting material to product peaks.

Table 4. Final optimization of the asymmetric system

Entry	[Fe]	Silane	Solvent	Time (h)	Yield (%) ^a	er ^b
1	Fe(acac) ₃	PhSiH ₃	dioxane	72	26	61:39
2	Fe(dpm) ₃	PhSiH ₃	dioxane	72	39	60:40
3	Fe(dibm) ₃	PhSiH ₃	dioxane	72	38	63.5:36.5
4	Fe(dibm) ₃	PhSi(OiPr) ₂ H ₂	dioxane	24	63	58.5:41.5
5	Fe(acac) ₃	PhSiH ₃	MTBE	72	65	60:40
6	Fe(dibm) ₃	PhSi(OiPr) ₂ H ₂	MTBE	24	74	61:39

^aPercent yield determined by GC-FID with a calibration curve. ^bEnantiomeric ratio (er) determined by HPLC with a chiral stationary phase. Peaks reported in order of elution.

increased yield, Fe(dibm)₃ additionally provided a slight boost in enantioinduction (Table 4, entries 2-3). This result indicates that iron may be involved in the enantiodetermining step, which is consistent with our earlier hypothesis that it is an iron–thiol complex that engages the transient radical. See SI for additional optimization of the metal catalyst.

Next, we considered the choice of silane. As in the mechanistic studies of the racemic reaction, changing to PhSi(OiPr)₂H₂ improved the asymmetric method to increase both yield and rate (Table 4, entry 3 vs 4). A variety of other silanes provided minimal to no conversion (see SI). Additionally, we tested methyl *tert*-butyl ether (MTBE) and observed a boost in yield of formation of **4d** (Table 4, entry 5). The effects of all three changes were additive, with the highest yield resulting from Fe(dibm)₃, PhSi(OiPr)₂H₂, and MTBE with no significant change in er (Table 4, entry 6). We moved forward with these reaction conditions for an assessment of the impact of variations to the substrate on the overall reaction efficiency and selectivity.

We also evaluated the internal olefin presented in Table 5, conscious of the possible impact of trisubstitution on the reaction selectivity. Gratifyingly, we observed a significant level of enantioselectivity (25:75 er) for the hydrogenation upon changing the ligand from acacH to dibmH. This further supports the hypothesis that iron is present in the enantiodetermining step (H-atom transfer from an iron(II) thiol complex). A change of the solvent system to 95:5 MTBE:EtOH led to a shorter reaction time and higher er, the latter of which is consistent with our spectroscopic studies indicating that iron(II) thiol binding may be more favorable in less polar solvents. Additionally, we screened the alternate carbohydrate-derived thiols using the internal olefin and found similar trends, with the highest er still provided by **C1** (see SI).

Having identified a chiral thiol catalyst, **C1**, and optimized reaction conditions that led to observation of meaningful er values, we assessed the mutual influences of different substrate features on selectivity with a number of prochiral substrates (Scheme 7). Namely,

Table 5. Screening conditions for internal olefin

Entry	[Fe]	Silane	Solvent	Time	Yield (%) ^a	er ^b
1 ^c	Fe(acac) ₃	PhSiH ₃	dioxane	7 days	10	37.5:62.5
2	Fe(dibm) ₃	PhSi(OiPr) ₂ H ₂	dioxane	72 h	10	30:70
3	Fe(dibm) ₃	PhSi(OiPr) ₂ H ₂	MTBE	24 h	13	25:75

^aPercent yield determined by GC-FID with a calibration curve. ^bEnantiomeric ratio (er) determined by HPLC with a chiral stationary phase. Peaks reported in order of elution. ^cPercent conversion to product determined by GC-FID as the crude ratio of starting material to product peaks.

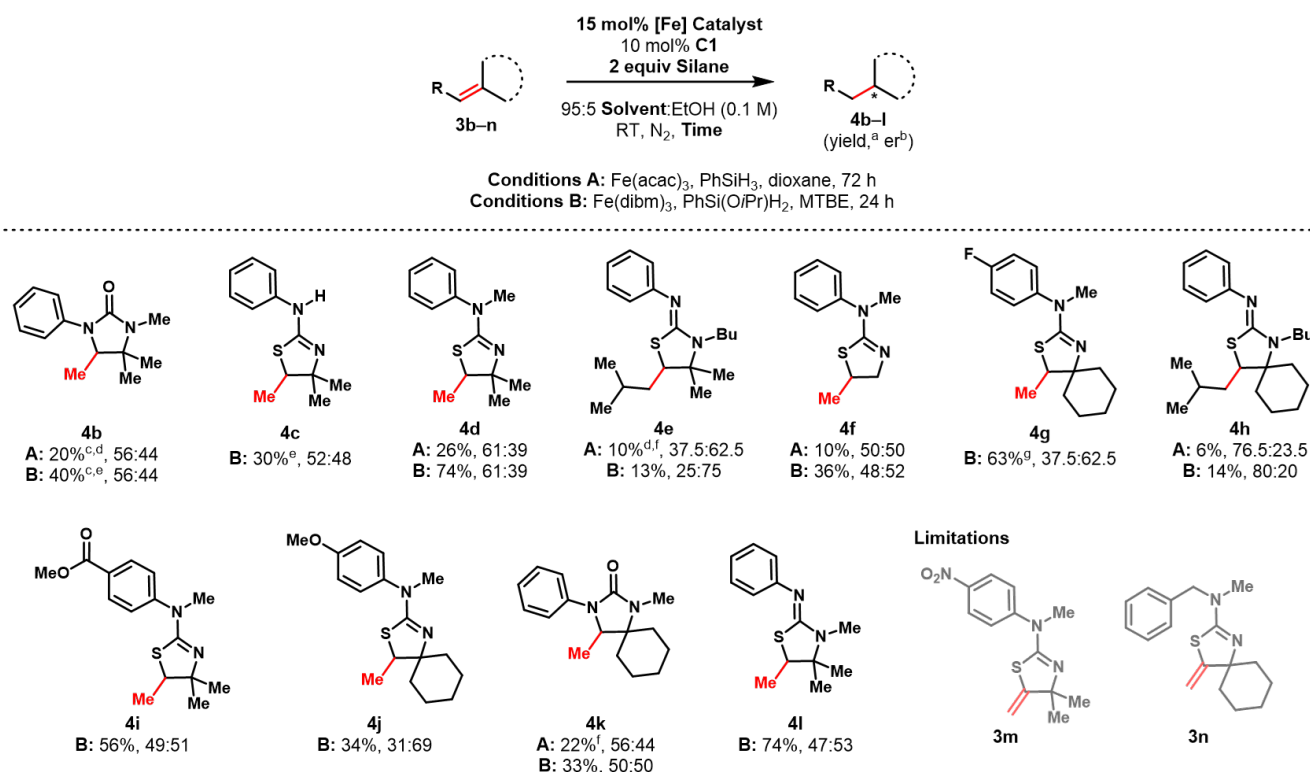
we tested a variety of thiazolidines as well as two cyclic ureas, with assorted functional groups and substituents of differing steric demand. In general, we examined two sets of conditions as defined in Scheme 7. In Conditions A, we used Fe(acac)₃, PhSiH₃, and dioxane, whereas in Conditions B, we used Fe(dibm)₃, PhSi(OiPr)₂H₂, and MTBE as defined by the mechanistically-guided optimization. We found that Conditions B resulted in a near-uniform yield increase across substrates and similar-to-increased er, in comparison to original Conditions A. These improvements highlight the ability of our mechanistic investigations to improve the enantioselective catalysis.

The minimal enantioinduction afforded by the free methylene and terminal olefin of **3f** (**4f**, 48:52 er) highlights that a fully substituted center adjacent to the olefin is necessary for notable enantioselectivity. In contrast to **3f**, unambiguous selectivity was observed for both fully substituted products **4d** (61:39 er) and **4g** (37.5:62.5 er). We further observe increased net enantioinduction when comparing the dimethyl-substituted thiazolidine (**4e**, 25:75 er) to the slightly bulkier spirocyclohexane (**4h**, 80:20 er), though the effect is modest. The most significant variable is the steric bulk from an internal olefin, evidenced by **3e** (producing **4e**, 25:75 er) and **3h** (producing **4h**, 80:20 er) exhibiting the highest enantioselectivity of all the tested substrates. Unfortunately, these bulky substrates also provided the lowest yields, and additional optimization would be required to increase the synthetic utility in these cases. Overall, the enantioinduction is influenced strongly by steric effects for this hydrogenation system.

Results with a number of other substrates (products **4b**, **4c**, **4i**, **4j**, **4k**, **4l**) are also presented in Scheme 7. These examples reveal a range of yields and er values that could provide starting points for future optimization with the compatibility of cHAT with Fe-based catalysis now firmly established.

There are limitations, as shown by two substrates that did not result in desired product formation under the reaction conditions.

Scheme 7. Substrate scope



^aPercent yield determined by GC-FID with a calibration curve. ^bEnantiomeric ratio (er) determined by HPLC with a chiral stationary phase. Peaks reported in order of elution. ^cReaction solvent: 95:5 benzene:EtOH. Enantiomeric ratio (er) determined by GC-FID with a chiral stationary phase. Peaks reported in order of elution. ^dPercent conversion to product determined by GC-FID as the crude ratio of starting material to product peaks. ^eReaction time 72 h. ^fReaction time 7 days. ^gYield determined by ¹H NMR with 1,2,4,5-tetramethylbenzene as the internal standard.

Substrate **3m** contains a nitro group that is likely to be reduced under our reaction conditions as observed in similar mHAT reaction conditions.³⁴ By contrast, **3n** led to only recovered starting material, which we tentatively attribute to the incompatibility of the *N*-benzyl substituent noted above in Scheme 5.

CONCLUSIONS

Here, mechanistic studies have been employed to advance the hydrogenation of unactivated olefins via cHAT. The compatibility of chiral thiol catalysts with these Fe-catalyzed reactions is a central finding, supported by the first observations of appreciable enantioinduction by iron-based catalysts under mHAT conditions. Kinetic studies of the reaction employing achiral catalysts show that the rate is zero-order with respect to all reagents except silane. Solvolysis studies with PhSi(O*i*Pr)₂H₂ suggest that PhSi(OEt)₂H₂ is faster in the hydrogenation reaction than PhSi(O*i*Pr)₂H₂. These both indicate that formation of the [Fe^{III}]-H intermediate is the turnover limiting step, and the pseudo-zero order dependence on iron concentration may be explained by the observed catalyst deactivation. From our kinetic studies, spectroscopic work, and computations, we propose a mechanism for cHAT that includes iron(II) thiol binding and transfer of H atom from the iron-bound thiol to the alkyl radical for PCET delivery of the second hydrogen atom in the enantiodetermining step. This forms an iron(III)-thiolate intermediate, which was observed by Mössbauer spectroscopy. We used these insights to explore the asymmetric hydrogenation of thiazolidines containing

prochiral olefins, employing a commercially available glucose-derived chiral thiol catalyst. The mechanistic exploration of this system guided our choice of nonpolar solvent mixtures, bulkier ligands, and a more reactive silane to ultimately enhance the yield, rate, and er in several cases. Exploration of the substrate scope suggests that the degree of enantioinduction is substrate-dependent and is more sensitive to steric environment than to non-covalent interactions.

This work adds to the small but growing number of asymmetric mHAT reactions enabled by small-molecule catalysts, and provides, to the best of our knowledge, the first demonstration of asymmetric hydrogenation via iron-catalyzed mHAT. Further, it shows the potential for cooperative reactivity between iron and thiols. The compatibility of chiral thiol catalysts with these Fe-catalyzed reactions creates an exciting opportunity for the development of novel asymmetric iron-catalyzed mHAT reactions.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website.

Synthetic procedures, experimental details, kinetic data, spectroscopic data, characterization data, NMR spectra, chiral HPLC chromatograms, X-ray crystallographic data, computational details, and additional screening results (PDF)

Raw data (ZIP)
X-ray data for **3c**, **3g**, **3h**, **3k**, and **3l** (CIF)

Accession Codes

CCDC 2304692–2304696 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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Graphical Abstract

