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Article

Kinetics of H· Transfer from $CpCr(CO)_3H$ to Various Enamides: Application to Construction of Pyrrolidines

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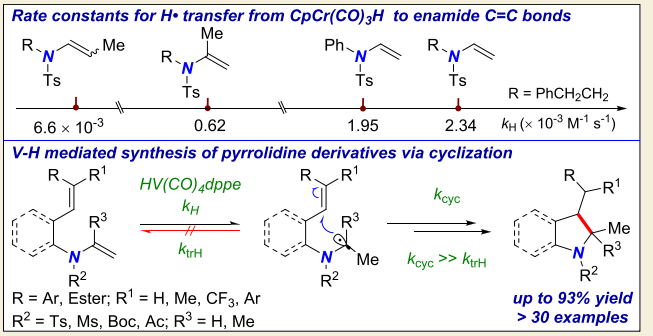
ABSTRACT: The rate constants k_H (k_D) have been determined at 27 °C for H· (D·) transfer from $CpCr(CO)_3H(D)$ to the C═C bonds of various enamides. This process leads to the formation of α-amino radicals. Vinyl enamides with *N*-alkyl and *N*-phenyl substituents have proven to be good H· acceptors, with rate constants close to those of styrene and methyl methacrylate. A methyl substituent on the incipient radical site decreases k_H by a factor of 4; a methyl substituent on the carbon that will receive the H· decreases k_H by a factor of 380. The measured k_H values indicate that these α-amino radicals can be used for the cyclization of enamides to pyrrolidines. A vanadium hydride, HV-$(CO)_4$(dppe), has proven more effective at the cyclization of enamides than Cr or Co hydrides—presumably because the weakness of the V−H bond leads to faster H· transfer. The use of the vanadium hydride is operationally simple, employs mild reaction conditions, and has a broad substrate scope. Calculations have confirmed that H· transfer is the slowest step in these cyclization reactions.



KEYWORDS: *rate constants, H· (D·) transfer, enamides, α-amino radicals, cyclization, pyrrolidines*

INTRODUCTION

Pyrrolidine derivatives are important in chemistry[1,2] and biology[3] and are found in natural products[4] and pharmaceutical molecules.[5,6] The synthesis of alkaloids that contain them (Figure 1A) has attracted significant attention from the scientific community.[7−9] They improve the solubility in water and other physiochemical properties of drugs like the ones in Figure 1B.[10,11]

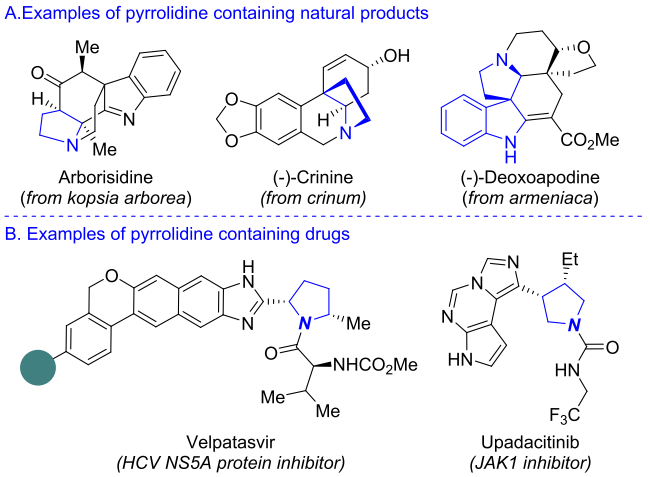


Figure 1. (A) Natural compounds featuring a pyrrolidine moiety. (B) Medicinal drugs containing a pyrrolidine moiety.

α-Amino radicals are useful in the construction of natural products and drugs that contain pyrrolidines.[12−16] Their synthesis has been reviewed by Dixon and co-workers,[13] who list three "classical" single-electron approaches: (a) oxidation and proton loss from an amine,[17−19] (b) oxidation and CO_2 loss from an amino carboxylate,[20,21] and (c) reduction and CO_2 loss from an amino ester[22,23] (Figure 2A). They note the recent popularity of imine reduction, often by photoredox methods (Figure 2B).[24,25]

We have made many radicals by H· transfer, to C═C,[26−29] exploiting a reaction that Sweany and Halpern[30] first reported in 1977. Such transfers have been used in hydrogenations,[31,32] hydroformylations,[33] radical polymerizations,[34] and intramolecular radical cyclizations.[35−39] Such cyclizations are powerful tools for the construction of complex molecular structures. The presence of heteroatoms increases the rate of such cyclizations;[40−42] replacing the C-4 methylene of the 6-

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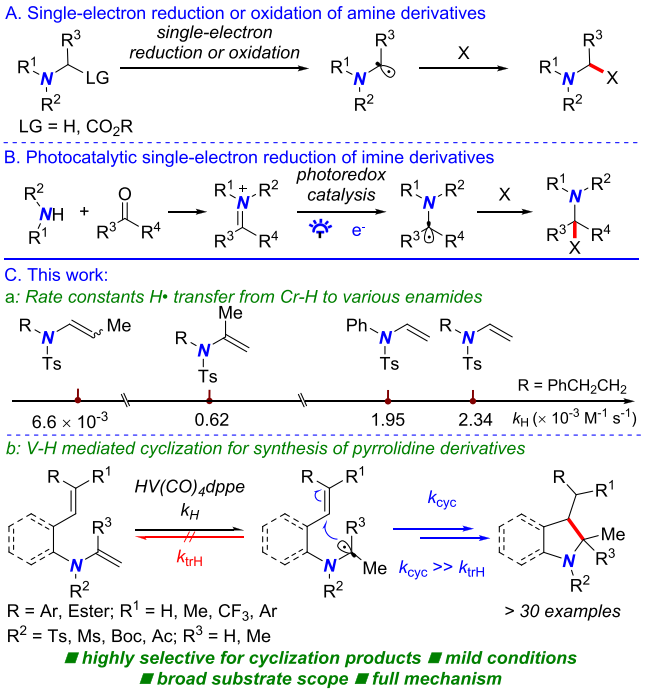


Figure 2. Generation of α-amino radicals and their application in synthesis. (A) Classic generation of α-amino radicals. (B) Generation of α-amino radicals by photoredox catalytic single-electron reduction of imine. (C) This work: (a) rate constant H· transfer from Cr−H to various enamides; (b) V−H-mediated cyclization for the synthesis of pyrrolidine derivatives.

hepten-2-yl radical by an oxygen is known to increase the rate of cyclization by a factor of 10.[40,41]

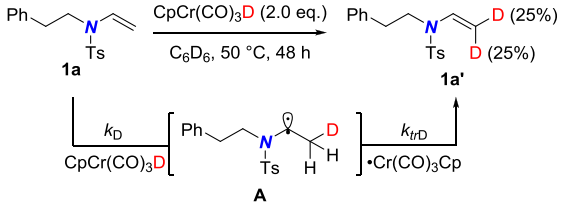
We have determined the rate constants for H· (D·) transfer from $CpCr(CO)_3H$ (D) to variously substituted enamides, including 4-methyl-*N*-phenethyl-*N*-vinylbenzenesulfonamide **1a**, 4-methyl-*N*-phenyl-*N*-vinylbenzenesulfonamide **1b**, 4-methyl-*N*-phenethyl-*N*-(prop-1-en-2-yl)benzenesulfonamide **1c**, and 4-methyl-*N*-phenethyl-*N*-(prop-1-en-1-yl)-benzenesulfonamide **1d** (Figure 2C, a). The rates depend on the substituents on C═C, much as they did for acrylates,[38] enol ethers,[29] and other olefins.[26−28] However, $CpCr(CO)_3H$ has proven unable to cyclize dienamides like **1e** with internal acceptors, so we have tried the vanadium hydride $HV(CO)_4$(dppe)—known to be faster at H· transfer.[28] (The V−H BDE is 57.5 kcal/mol, whereas the Cr−H bond in $CpCr(CO)_3H$ is 62.2 kcal/mol.) Overall, we report the conversion of enamides like **1**[43,44] to α-amino radicals and the cyclization of such radicals to pyrrolidine derivatives (Figure 2C, b). Computational studies have rationalized the effectiveness of $HV(CO)_4$(dppe) (Figure 2C, b).

RESULTS AND DISCUSSION

H/D Exchange between $CpCr(CO)_3D$ 2a and Enamides (1a−1d)

We began by treating the enamide **1a** (methyl-*N*-phenethyl-*N*-vinylbenzenesulfonamide) with 2.0 equiv of $CpCr(CO)_3D$ (**2a**) at 50 °C. After 48 h, we observed no hydrogenation but 25% H/D exchange on the terminal carbon, implying that there had been slow formation of the α-amino radical **A** by D• transfer from **2a** to the C═C bond of **1a** (Scheme 1). We obtained similar results with enamides 4-methyl-*N*-phenyl-*N*-vinylbenzenesulfonamide (**1b**), 4-methyl-*N*-phenethyl-*N*-(prop-1-en-2-yl)benzenesulfonamide (**1c**), and 4-methyl-*N*-phenethyl-*N*-(prop-1-en-1yl)benzenesulfonamide (**1d**). (All of the enamides are drawn in Figure 3.)

Scheme 1. H/D Exchange between Enamide 1a and $CpCr(CO)_3D$ 2a



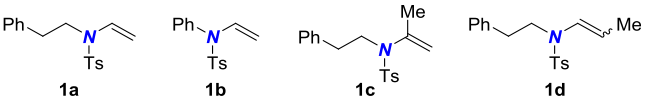
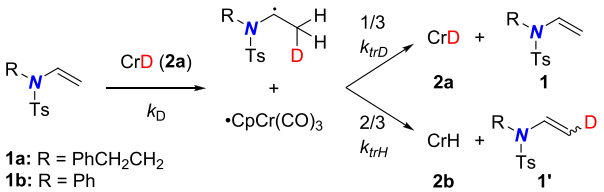


Figure 3. Enamides were studied as D· transfer acceptors.

We had previously measured rate constants (k_H) for H· transfer from $CpCr(CO)_3H$ to various C═C[26−28] and had found the results useful in predicting the relative H· acceptor abilities of these double bonds. The relative rate constants reflect the stabilities of the radicals formed. We therefore needed to determine the k_H values of our enamides.

When a solution of **2a** was treated with a large excess (>10 equiv) of **1a** (C_6D_6, 300 K), a vinyl ^{2}D signal appeared as we would expect from Scheme 2. We also saw exponential growth

Scheme 2. H/D Exchange between Enamides 1a and 1b and $CpCr(CO)_3D$ 2a



in the integral of the hydride NMR signal of $CpCr(CO)_3H$ (**2b**) (Figures S5−S8). From the time dependence of this integral, we got a pseudo-first-order rate constant k_{obs} (eq 1). We found that k_{obs} was a linear function of [**1a**] (Figure 4), which confirmed the second-order kinetics of the H/D exchange between **1a** and **2a**. From the slope of Figure 4, we learned k_1, a rate constant that reflects both the initial D·

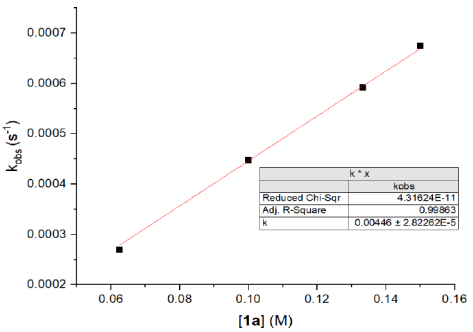


Figure 4. Plot of k_{obs} vs [**1a**] for D· transfer from **2a** to **1a** at 300 K in C_6D_6.

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abstraction from $CpCr(CO)_3D$ (**2a**) and the back-transfer of H· and D· (rate constants k_{trH} and k_{trD} in Scheme 2); it (k_1) is 4.46×10^{-3} M^{-1} s^{-1} at 300 K. To get k_D, we needed to divide k_1 by S (see eq 2), the fraction of the D· initially transferred that results in H· back transfer. As in our previous report,[26] the isotope effect k_{trH}/k_{trD} can be estimated as 3, so S is 6/7 from eq 3 and k_D is 5.20×10^{-3} M^{-1} s^{-1} at 300 K. If we estimate the kinetic isotope effect for H/D transfer from $CpCr(CO)_3H$ (k_{CrH}/k_{CrD} in eq 4) as 0.45 as in our previous work,[26] we obtain an estimate of k_H as 2.34×10^{-3} M^{-1} s^{-1} at 300 K.

$$\frac{d[\mathrm{CrH}]}{d_t} = k_1[\mathbf{1}][\mathrm{CrD}] = k_{obs}[\mathrm{CrD}] \quad (1)$$

$$k_1 = Sk_D \quad (2)$$

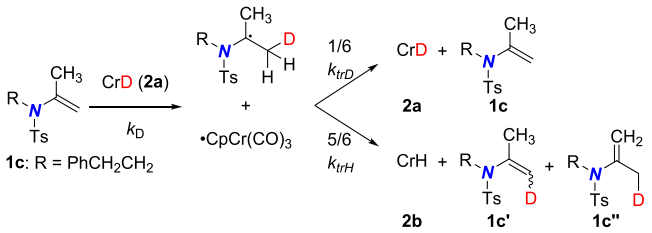
$$S = \frac{\left(\frac{2}{3}\right)k_{trH}[\mathrm{Cr}\cdot]}{\left(\frac{2}{3}\right)k_{trH}[\mathrm{Cr}\cdot] + \left(\frac{1}{3}\right)k_{trD}[\mathrm{Cr}\cdot]} = \frac{2\frac{k_{trH}}{k_{trD}}}{2\frac{k_{trH}}{k_{trD}} + 1} \approx \frac{6}{7} \quad (3)$$

$$k_H = k_D\frac{k_{CrH}}{k_{CrD}} \quad (4)$$

Similarly, when **2a** was treated with a large excess of **1b** in C_6D_6 at 300 K, we found that k_{obs} was a linear function of [**1b**] (Figures S10–S14) and that k_1 for **1b** is 3.72×10^{-3} M^{-1} s^{-1} at 300 K. Using S from eq 3, we find that for **1b**, k_D is 4.34×10^{-3} M^{-1} s^{-1}, and k_H can be estimated from eq 4 as 1.95×10^{-3} M^{-1} s^{-1}.

When **2a** was treated with excess **1c** in C_6D_6 at 300 K, analogous effects were observed in the ^1H and ^2D NMR spectra (Figures S15–S18), as we would expect from the mechanism in Scheme 3. Variation of [**1c**] established that k_{obs}

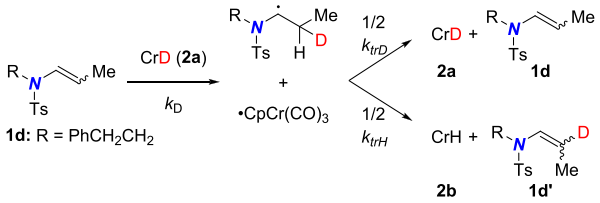
Scheme 3. H/D Exchange between the Enamide 1c and $CpCr(CO)_3D$ 2a



was a linear function of [**1c**] (Figure S19), implying a k_1 of 1.29×10^{-3} M^{-1} s^{-1} at 300 K. If we now use eq 5 to estimate S (15/16), we find that k_D is 1.38×10^{-3} M^{-1} s^{-1}, resulting in an estimate for k_H of 0.62×10^{-3} M^{-1} s^{-1}.

Preliminary experiments showed that **1d** reacted more slowly with **2a** than had **1a**, **1b**, and **1c**, so we employed larger concentrations (2, 3, and 3.5 M, all >10 equiv) of **1d** to determine its H· transfer rate constant and observed the effects we expected from the operation of Scheme 4 (Figures S20–S22). A plot of k_{obs} vs [**1d**] implied $k_1 = 1.10 \times 10^{-5}$ M^{-1} s^{-1} (Figure S23). If we use eq 6 to estimate the fractional probability S as 3/4, we find that k_D is 1.47×10^{-5} M^{-1} s^{-1}, resulting in an estimate for k_H of 6.6×10^{-6} M^{-1} s^{-1}.

Scheme 4. H/D Exchange between Enamide 1d and $CpCr(CO)_3D$ 2a

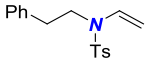
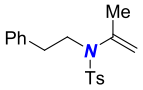
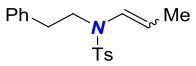
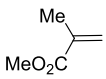


$$S = \frac{\left(\frac{5}{6}\right)k_{trH}[\mathrm{Cr}\cdot]}{\left(\frac{5}{6}\right)k_{trH}[\mathrm{Cr}\cdot] + \left(\frac{1}{6}\right)k_{trD}[\mathrm{Cr}\cdot]} = \frac{5\frac{k_{trH}}{k_{trD}}}{5\frac{k_{trH}}{k_{trD}} + 1} \approx \frac{15}{16} \quad (5)$$

$$S = \frac{\left(\frac{1}{2}\right)k_{trH}[\mathrm{Cr}\cdot]}{\left(\frac{1}{2}\right)k_{trH}[\mathrm{Cr}\cdot] + \left(\frac{1}{2}\right)k_{trD}[\mathrm{Cr}\cdot]} = \frac{\frac{k_{trH}}{k_{trD}}}{\frac{k_{trH}}{k_{trD}} + 1} \approx \frac{3}{4} \quad (6)$$

Looking at the k_H values collectively (Table 1), we can see that enamides **1a**, **1b**, and **1c** are excellent H· acceptors. The

Table 1. Rate Constants k_H of H· Transfer from $CpCr(CO)_3H$ to Various Enamides at 300 K[a]

	Enamides	k_H ($\times 10^{-3}$ M^{-1} s^{-1})	Relative rate
1a		2.34	3.8
1b		1.95	3.1
1c		0.62	1
1d		6.6×10^{-3}	0.01
Styrene		2.86[b]	4.6
MMA		1.82[b]	2.9

[a]Obtained from measured k_D by eq 4. [b]Extrapolation from activation parameters of our previous work.[26]

reactivities of **1a** and **1b** are higher than that of methyl methacrylate, and **1a**, **1b**, and **1c** have reactivities close to that of styrene. The *N*-alkyl-substituted enamide **1a** accepts H· more readily than the *N*-phenyl **1b**, whereas the methyl substituent on the incipient radical site in **1c** decreases k_H (by a factor of 3.8). The methyl substituent on the hydrogen acceptor carbon in **1d** slows the reaction by a factor of 380.

Cyclization of Enamides

We then wanted to see if enamides such as **1** could be employed in radical cyclization reactions. We needed a radical acceptor that would not compete with our enamide as an H· acceptor and considered the phenyl-substituted olefin in **1e** (Table 2). However, neither gave any cyclization product when treated with catalytic $CpCr(CO)_3H$ (5%) or $Co(dmgBF_2)_2(THF)_2$ (5%) under H_2 conditions[45] at 50 °C (entries 1 and 2). Treatment of **1e** with Co^{II}-salen/Ph_2SiH_2

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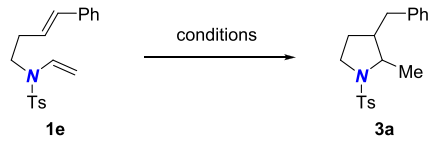
Table 2. Screening Conditions for Cyclization of Enamides[a]



1e 3a

entry	[M]	solvent	temp. (°C)	yield (%)[b]
1[c]	$HCr(CO)_3Cp$	PhH	50	n.d.
2[d]	$Co(dmgBF_2)_2(THF)_2$	PhH	50	n.d.
3	Co^{II}-salen/Ph_2SiH_2	PhH	50	n.d.
4	$HV(CO)_4$dppe	PhH	23	38
5	$HV(CO)_4$dppe	PhH	50	55
6	$HV(CO)_4$dppe	PhH	85	74
7	$HV(CO)_4$dppe	Toluene	110	48
8	$HV(CO)_4$dppe	THF	85	36
9	$HV(CO)_4$dppe	MeCN	85	60

[a]Enamide **1e** (0.05 mmol, 1.0 equiv), [$HV(CO)_4$dppe] (2.1 equiv), solvent (2 mL, 0.025M), 24 h. [b]^{1}H NMR yields. [c]$CpCr(CO)_3H$ (5%), 80 psi H_2, 3 days. [d]$Co(dmgBF_2)_2(THF)_2$ (5%), 80 psi H_2, 3 days. CoII-salen: (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II).

yielded a mixture of unidentified products (entry 3). We then decided to try a hydride with a weaker M−H bond, and the obvious candidate was $HV(CO)_4$(P−P) (P−P = chelating phosphine ligand).[28,29] The V−H bond in the dppe hydride is only 57.5 kcal/mol, whereas the Cr−H bond in $CpCr(CO)_3H$ (**2b**) is 62.2 kcal/mol.[28] Indeed, $HV(CO)_4$(dppe) (**2c**) gave a decent (55%) yield of the cyclization product **3a** at 50 °C (entry 5) and a higher yield (74%) at 85 °C (entry 6). Neither the methyl-substituted olefin in **1f** nor the isopropyl-substituted one in **1g** (see the Supporting Information for details) gave any cyclization product under the same conditions.

We next explored the scope of intramolecular cyclizations with **2c**. As Figure 5 shows, a broad array of enamides are suitable substrates. Most substituted phenyls give good results, producing **3b**−**3j** in 61−77% yields with electron-donating alkoxide (**3b**) or amine (**3c**) substituents, electron-deficient trifluoromethyl (**3d**), 3,4-difloro (**3h**), or difluorobenzodioxole (**3i**) substituents, or a sterically hindered 2-methyl (**3j**) substituent or with functional groups such as bromo (**3e**), thioether (**3f**), or carbomethoxy (**3g**). The cis diastereomer is always the major product (as expected from the calculations below).

We were pleased to find that when the phenyl group on the carbon radical acceptor C═C was replaced with a polycyclic arene such as naphthalene (**3k**) or anthracene (**3l**), cyclization still occurred in satisfied yield. Enamides that contain medicinally privileged heterocyclic arenes, including indole, carbazole, thiophene, pyrazole, and pyridine, can tolerate our reaction conditions and give cyclized products **3m**−**3r**. Enamides that contain two substituents, including Ph/Ph, Ph/Me, Ph/CF_3, and Ph/pyridine, on the isolated olefin can provide pyrrolidine derivatives **3s**−**3v** in moderate to excellent yields. The dimethyl pyrrolidine derivative **3w** can be obtained in 67% yield from the corresponding enamide. (During this reaction, we observe 5% hydrogenation of the isolated C═C.) When an *α*,*β*-unsaturated ester serves as the acceptor for the carbon radical from an enamide, an ester-containing pyrrolidine derivative such as **3x** can be obtained in 93% yield.

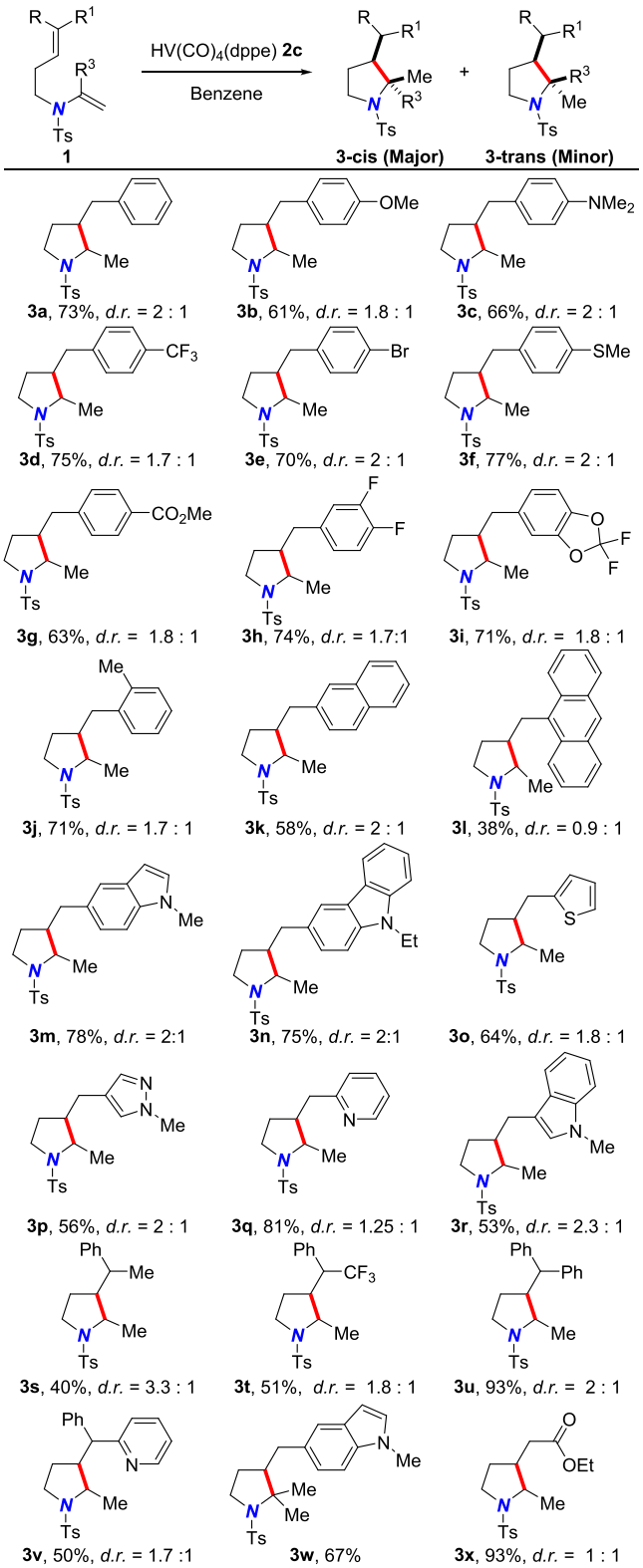


Figure 5. Scope of the cyclization of *N*-alkyl enamides. Conditions: enamide (0.05 mmol, 1.0 equiv), **2c** (2.1 equiv), and benzene (0.025 M), 85 °C, 15 h. Isolated yields.

Table 1 shows that the *N*-aryl enamide **1b** has a rate constant k_H similar to that of the *N*-alkyl enamide **1a**, and the same result is obtained when we compare *N*-aryl enamides and *N*-alkyl enamides in general. Thus, we have designed and synthesized a series of *N*-2-styrylphenyl enamides **1ae**−**1aj** and

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used them to construct (under ambient conditions, in good yields) the indoline derivatives in Figure 6 (**3y**–**3ad**). This

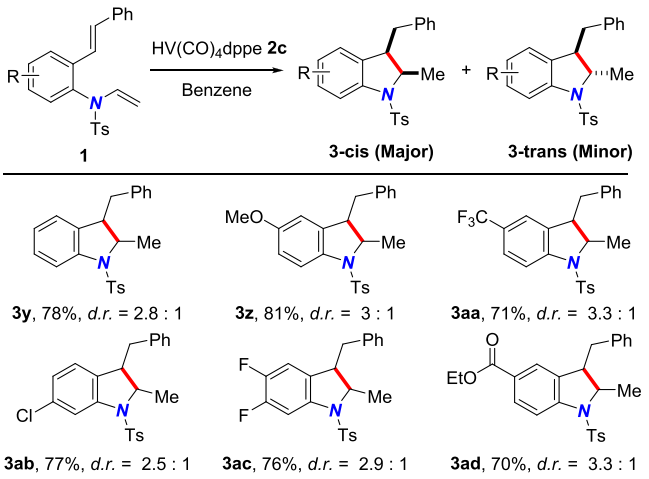

Figure 6. Scope of the cyclization of the *N*-alkyl enamides. Conditions: enamide (0.05 mmol, 1.0 equiv), **2c** (2.1 equiv), benzene (0.025 M), 85 °C, 15 h. Isolated yields.

reaction also accommodates a broad range of substituents on its aromatic ring, including electron-rich (**3z**) and electron-deficient (**3aa** and **3ac**) groups and sensitive functional groups such as chloro (**3ab**) and ester (**3ad**).

Finally, we extended our reaction to the other *N*-protecting groups in Figure 7. The *N*-Ms-, *N*-Boc-, and *N*-acyl enamides

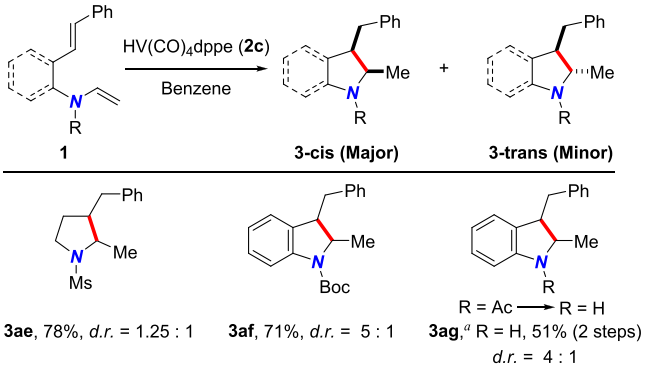

Figure 7. Scope of cyclization of various *N*-protected enamides. Conditions: enamides (1.0 equiv), **2c** (2.1 equiv), and benzene (0.025 M), 85 °C, 15 h. [a]See the Supporting Information for details.

cyclized smoothly with stoichiometric $HV(CO)_4(dppe)$ to provide the pyrrolidine derivatives **3ae**–**3ag**. The *N*-acyl was easily removed (one pot) after cyclization,[46] giving a 51% yield (two steps in one pot) of **3ag**.

Mechanism

We have observed the reaction of enamide **1e** (0.025 M) with stoichiometric $HV(CO)_4(dppe)$ (Figure 8). The reaction is almost complete (93% conversion of **1e**) within 5 h. The faster rate with $HV(CO)_4(dppe)$ is the result of its weaker V–H bond, which has a BDE of 57.5 kcal/mol (62.2 kcal/mol of the Cr–H bond in $CpCr(CO)_3H$). As radical cyclizations are relatively fast,[47,48] we believe that HAT is the rate-determining step of our enamide cyclization reactions.

We next performed density functional theory (DFT) calculations to explore the reaction mechanism. DFT-

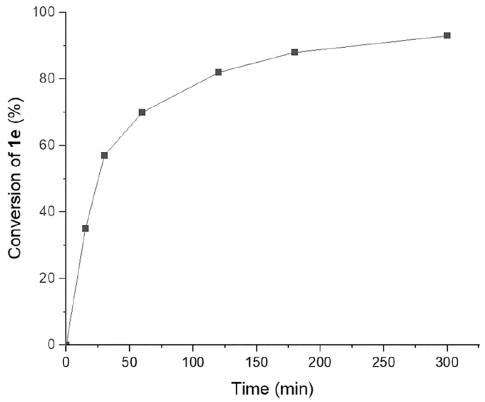

Figure 8. Reaction of **1e** with $HV(CO)_4(dppe)$. Conditions: **1e** (0.025 mmol, 1 equiv), $HV(CO)_4(dppe)$ (2.0 equiv), benzene (0.025 M), 85 °C, 0–5 h.

computed results have ruled out unfavorable reaction pathways (see Figures S1 and S2 for more details) and have indicated that this vanadium hydride-promoted cyclization process is initiated by HAT. As shown in Figure 9, $HV(CO)_4(dppe)$

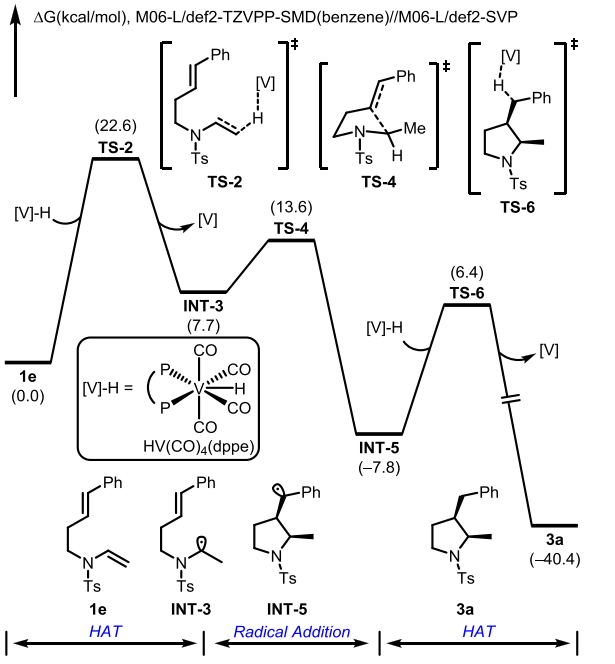

Figure 9. Mechanistic hypothesis. DFT-computed free energy diagram of the vanadium hydride-promoted cyclization process of enamide **1e**.

delivers a hydrogen atom to enamide **1e** through **TS-2** to give $V(CO)_4(dppe)$ and α-amino radical species **INT-3**, with a free energy barrier of 22.6 kcal/mol. Then, **INT-3** undergoes a facile intramolecular radical addition step via **TS-4** to irreversibly generate the benzyl radical **INT-5**. Next, the benzyl radical abstracts a hydrogen atom from another molecule of $HV(CO)_4(dppe)$ through **TS-6** to liberate the pyrrolidine product **3a**.

SUMMARY

We have measured the rate constants k_H (k_D) of H· (D·) transfer from $CpCr(CO)_3H$ (D) to various substituted enamides. Both *N*-alkyl- and *N*-phenyl-substituted enamides

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are excellent H· acceptors, close to styrene and methyl methacrylate. A methyl substituent on the incipient radical site decreases k_H by a factor of 3.8, and a methyl substituent on the H· acceptor site decreases k_H by a factor of 380. These rate constants k_H reflect the stability of the α-amino radicals that are formed and provide guidelines for use of enamides in synthetic transformations. As a result of the k_H studies, we have developed the first vanadium-promoted synthesis of pyrrolidine derivatives from enamides that is mild, fast, and highly selective, but $CpCr(CO)_3H/H_2$, $Co(dmgBF_2)_2(THF)_2/H_2$, and Co^{II}-salen/Si−H do not facilitate the reductive cyclization of enamides. We also performed DFT calculations on the reaction mechanism. Computational results indicate that the HAT to the enamide is the rate-determining step.

METHODS

General Procedure for NMR Kinetic Measurements

All experiments were performed at 500 MHz. A stock solution of $CpCr(CO)_3D$ (between 0.0625 and 3.5 M) in C_6D_6 was prepared with an internal standard (hexamethylcyclotrisiloxane), placed in a J-Young tube, and frozen under an atmosphere of argon. A C_6D_6 solution containing at least a 10-fold excess of enamide was then added and frozen under argon atop the first solution. The tube was allowed to thaw, and its contents were mixed before it was placed in the probe of NMR. The integration of the hydride of the $CpCr(CO)_3H$ peak relative to that of the internal standard was recorded as a function of time. Two pulses were used for each kinetic point, with indicated time between the two pulses. The kinetic data were fit to an exponential, and the rate constant and infinity point were adjusted for the best fit (eq 7).

$$[Cr-H]_t = [Cr-H]^{\infty} + ([Cr-H]_0 - [Cr-H]]^{\infty}) \exp(-k_{obs}t) \quad (7)$$

General Procedure for Cyclization of Enamides

An oven-dried vial equipped with a stir bar was charged with an enamide substrate (neat, 1.0 equiv) and $HV(CO)_4$(dppe) (2.1 equiv). Benzene (0.025 M) was added, and the reaction mixture was stirred at 85 °C for an indicated time. After the indicated time, the reaction mixture was quenched with NH_4Cl (aq., 1.0 M, 2 mL) and diluted with EtOAc (10 mL), and the organic layer was washed with water (1 × 10 mL) and brine (1 × 10 mL), dried, and concentrated. A sample was analyzed by ^1H NMR ($CDCl_3$, 400 or 500 MHz) to obtain conversion, yield, and selectivity using an internal standard. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

DFT Calculations

Computational studies were performed at the M06-L/def2-TZVPP-SMD(benzene)//M06-L/def2-SVP level of theory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00529.

Experimental information and procedures, characterization data of compounds, copies of NMR spectra, and DFT calculation details (PDF)

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Author Contributions

G.L., J.R.N., and X.H. conceived the project. G.L., S.S., and J.Q. conducted the experiments. G.X. and X.H. carried out the DFT calculations. All authors analyzed and interpreted the results. G.L., J.R.N., and X.H. wrote the manuscript.

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Notes

The authors declare no competing financial interest.

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