JOC The Journal of Organic Chemistry

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Can Primary Arylamines Form Enamine? Evidence, α-Enaminone, and [3+3] Cycloaddition Reaction

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Cite This: J. Org. Chem. 2021, 86, 14617−14626 Read Online

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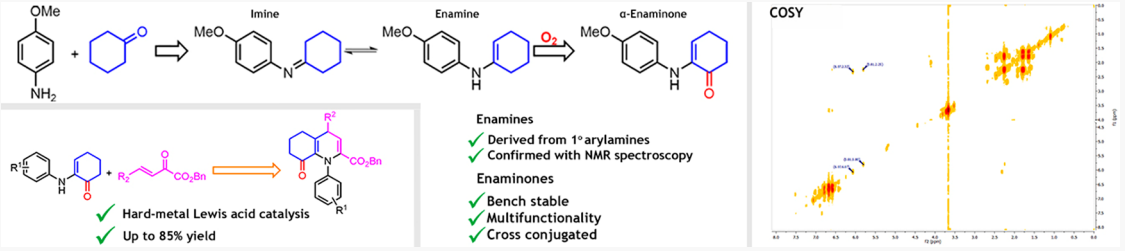


ABSTRACT: The formation of enamine from primary arylamines was detected and confirmed by nuclear magnetic resonance spectroscopy. The presence of a radical quencher, e.g., (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl, was found to be essential for the detection of enamine formation. A direct synthesis of α-enaminones from primary arylamines and ketones was also developed. Mechanistic investigation of α-enaminone formation suggests that an amine radical cation generated through O_2 singlet energy transfer was involved in initiating α-enaminone formation. The reactivity and utility of α-enaminones were explored with a [3+3] cycloaddition reaction of enones affording dihydropyridines in good yields (58−85%). α-Enaminones displayed a set of reactivities that is different from that of enamines. The knowledge gained in this work advances our basic understanding of organic chemistry, providing insights and new opportunities in enamine catalysis.

INTRODUCTION

Enamine catalysis has played a major role in organocatalysis.[1−4] Traditionally, secondary (2°) aliphatic amines serve as the amine catalysts in enamine catalysis (Figure 1). It is commonly accepted that aliphatic amines activate aldehydes/ketones through the formation of enamine. As it is the important reaction intermediate, the elusive presence of the enamine intermediate based on 2° amine (i.e., proline) was not confirmed until recently.[5,6] Primary (1°) amines have also often been used in enamine catalysis.[7−15] However, evidence of the existence of enamine intermediates based on 1° amines has never been reported. Primary amines form imines with aldehydes/ketones, which is commonly taught in organic chemistry. Isomerization of the imine intermediate to form enamine is theoretically possible. However, the enamine intermediate derived from a 1° amine is expected to be extremely difficult to detect (Figure 1). In our endeavor to develop cooperative enamine−hard metal Lewis acid catalysis,[16−21] we introduced a reversed soft−hard strategy in which 1° arylamines such as aniline take the place of aliphatic amines in enamine catalysis in combination with hard metal Lewis acid catalysis (Figure 1). We suspected that enamine derived from 1° arylamines could be more stable than its aliphatic counterpart due to its cross-conjugation to the aryl ring and

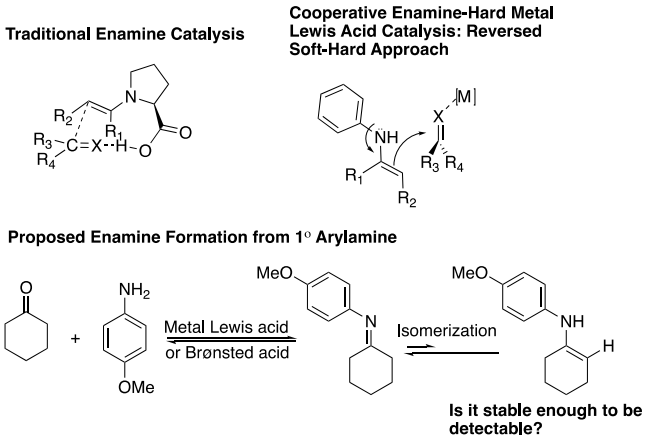


Figure 1. Enamine catalysis, cooperative enamine−hard metal Lewis acid catalysis, and formation of enamine from 1° arylamine.

Received: June 21, 2021
Published: October 5, 2021

https://doi.org/10.1021/acs.joc.1c01462
J. Org. Chem. 2021, 86, 14617−14626

thus could be detectable. Herein, we report our preliminary investigation of the formation of enamine from 1° arylamine using NMR spectroscopy. It was found that in the presence of a radical scavenger, e.g., (2,2,6,6-tetramethylpiperidin-1-yl)-oxidanyl (TEMPO), enamine formation was detected and confirmed via ^{1}H, COSY, and HSQC NMR spectroscopy. The findings in this work will provide new insights into enamine catalysis and will advance our basic understanding of organic chemistry and other scientific research related to enamines.

In this work, we also introduce a direct synthesis of α-enaminones from cyclic ketones and primary arylamines catalyzed by a Brønsted or metal Lewis acid (Figure 2).

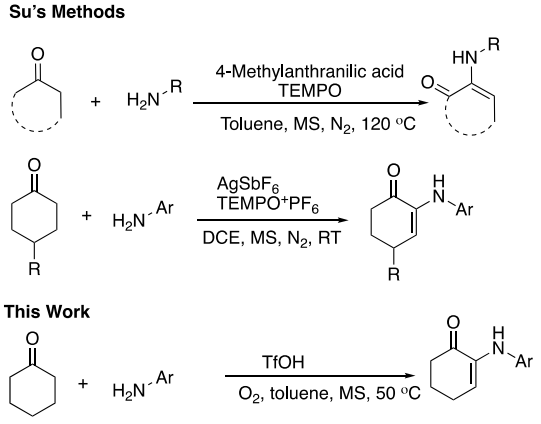


Figure 2. Direct synthesis of α-enaminones.

Enaminones are important structural motifs in organic synthesis as they serve as versatile synthetic intermediates for constructing a wide variety of heterocycles such as pyrroles, pyrrolines, and piperidines.[22−31] The typical synthesis of α-enaminones is through electrophilic α-amination of ketones, which involves the multiple-step preparation of nitrogen precursors and subsequent transformations.[32] Direct synthesis of α-enaminones through ketone and amines was not available until very recently.[33−35] During this investigation, two direct approaches for the synthesis of enaminone were reported by the Su group (Figure 2).[33,35] In Su's methods, TEMPO$^+$PF$_6$ or TEMPO was used as an oxygen transfer reagent along with AgSbF$_6$ or 4-methylanthranilic acid as the catalyst, respectively. In our work, a metal Lewis acid or a Brønsted acid serves as the catalyst, and air or molecular oxygen serves as the oxidant. In sharp contrast to Su's method, TEMPO turned out to be a quencher for this reaction. The information obtained in this work offers new perspectives for this interesting organic transformation.

The reactivities and utility of α-enaminones were also investigated. α-Enaminones possess both nucleophilic (enamine and amine) and electrophilic (enone) characteristics (Figure 3). The multifunctional nature of α-enaminones makes them attractive substrates for the construction of complex architectures.[36−45] However, the reactivities of α-enaminones remain largely unexplored due to their difficult accessibility. The concise synthetic methods developed for enaminones in the past two years offer an excellent opportunity to investigate this interesting class of compounds. In this work, we report that α-enaminones displayed nucleophilic properties to react with enones in a novel [3+3] cycloaddition reaction affording dihydropyridines in good yields (Figure 3).

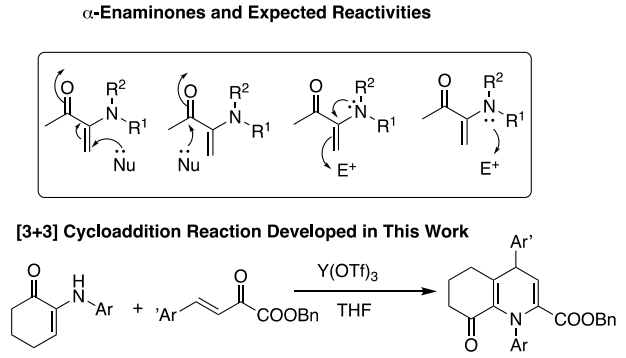
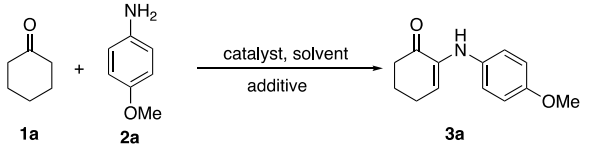


Figure 3. α-Enaminone and its expected reactivities and [3+3] cycloaddition reaction.

RESULTS AND DISCUSSION

Direct Enaminone Formation. During our investigation of cooperative enamine−hard metal Lewis acid catalysis, we observed that, when *p*-methoxyaniline was mixed with cyclohexanone in the presence of Y(OTf)$_3$, a minor product along with the imine intermediate was formed. To our surprise, this minor product was identified as α-enaminone **3a** (Table 1, entry 1). The occurrence of this reaction suggests that enamine was likely formed as an intermediate and air serves as an oxidant in this reaction. This result prompted us to investigate the possibility of formation of enamine from 1° arylamine. One convenient and convincing way is to track the reaction with ^{1}H

Table 1. Optimization of the Reaction Conditions for α-Enaminone Formation[a]



entry	catalyst (10 mol %)	solvent	additives	T (°C)	t (h)	yield[c] (%)
1	Y(OTf)$_3$	THF	–	RT	6	4
2	Y(OTf)$_3$	THF	air	RT	22	11
3[b]	Y(OTf)$_3$	THF	air, 4 Å MS	RT	22	22
4[b]	Y(OTf)$_3$	THF	O$_2$, 4 Å MS	RT	22	28
5[b]	Sc(OTf)$_3$	THF	O$_2$, 4 Å MS	RT	22	52
6[b]	Yb(OTf)$_3$	THF	O$_2$, 4 Å MS	RT	22	27
7[b]	Fe(OTf)$_3$	THF	O$_2$, 4 Å MS	RT	22	18
8[b]	FeCl$_3$	THF	O$_2$, 4 Å MS	RT	22	23
9[b]	pTsOH	Tol	O$_2$, 4 Å MS	RT	22	30
10[b]	TfOH	Tol	O$_2$, 4 Å MS	RT	22	46
11[b]	TfOH	Tol	O$_2$, 4 Å MS	50	22	64[d]
12[b]	Sc(OTf)$_3$	THF	O$_2$, 4 Å MS	50	22	24
13[b]	TfOH	Tol	O$_2$, 4 Å MS	reflux	22	19
14[b]	TfOH	Tol	air, 4 Å MS, PCC[e]	50	6	21
15[b]	TfOH	Tol	air, 4 Å MS, tBuOOH[e]	50	6	28
16[b]	TfOH	Tol	O$_2$, 4 Å MS, TEMPO[f]	50	22	4.7
17[b]	TfOH	Tol	O$_2$, 4 Å MS, ascorbic acid[f]	50	22	5.0

[a]Unless otherwise noted, 4.0 mmol of **1a** and 0.2 mmol of **2a** were used in the reaction. [b]With 28 mg of 4 Å MS added. [c]Estimated by ^{1}H NMR spectroscopy using dibromoethane as the internal standard. [d]Isolated yield. [e]At 10 mol %. [f]With 0.8 mmol.

https://doi.org/10.1021/acs.joc.1c01462
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NMR spectroscopy. If enamine is formed, a triplet peak representing the proton attached to the enamine double bond should appear at 4−6 ppm. However, when *p*-methoxyaniline was mixed with cyclohexanone in the presence of $Y(OTf)_3$ in $CDCl_3$, only very weak peaks belonging to α-enaminone-H appeared at 6.07 ppm. The expected $C(sp^2)$−H bond of enamine was not observed, which is likely due to the low yield of this reaction. We decided to optimize the reaction conditions to improve the yield first (Table 1). When air was bubbled through the reaction mixture in the presence of $Y(OTf)_3$ in THF, the yield of enaminone increased to 11% (entry 2). Inclusion of molecular sieves improved the yield to 22% (entry 3). When molecular O_2 was used, the yield was further improved to 28% (entry 4). While $Yb(OTf)_3$ gave a result similar to that of $Y(OTf)_3$, $Sc(OTf)_3$ significantly increased the yield to 52% (entries 6 and 5, respectively). Redox active $Fe(OTf)_3$ and $FeCl_3$ decreased the yield (entries 7 and 8, respectively). Stronger Brønsted acids were also used for this reaction. *p*-Toluenesulfonic acid (pTsOH) led to enaminone formation in 30% yield, and triflic acid (TfOH) turned out to be much more effective, giving **3a** in 46% yield in toluene (entries 9 and 10, respectively). When the reaction temperature was increased to 50 °C, the yield increased to 64% (entry 11). We also attempted the reaction with $Sc(OTf)_3$ at 50 °C; however, the yield decreased to 24% (entry 12). When the reaction was performed with TfOH at the refluxing temperature of toluene, the yield of **3a** decreased significantly (entry 13). Addition of extra oxidants such as pyridinium chlorochromate (PCC) and ^{t}BuOOH also decreased the yield (entries 14 and 15, respectively). When oxygen radical scavengers TEMPO and ascorbic acid were added, the reactions were almost quenched, generating **3a** in <5% yields (entries 16 and 17, respectively). These results are in sharp contrast with Su's work in which $TEMPO^+PF_6$ or TEMPO was used as an oxygen transfer reagent to facilitate the formation of α-enaminones,[33,35] reflecting a different mechanism being at play.

On the basis of these data, a mechanism involving an amine radical cation is proposed for α-enaminone formation. The reaction is initiated by an amine radical cation (**B**) generated through O_2 singlet energy transfer (SET) (Figure 4). Radical cation **B** reacting with enamine **A** derived from cyclohexanone (**1a**) and *p*-methoxyaniline (**2a**) through isomerization produces radical intermediate **C**. Intermediate **C** goes through another SET generating iminium ion **D**, which upon hydrolysis gives α-aminoketone **E**. α-Aminoketone **E** undergoes oxidative dehydrogenation to generate α-enaminone **3a**.

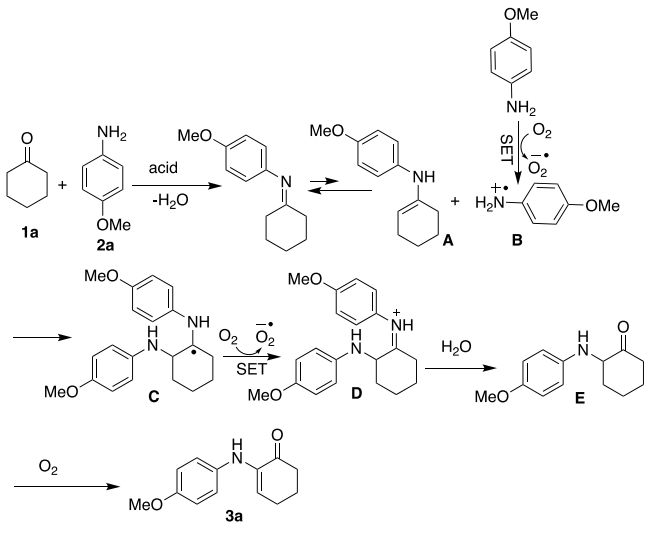

Figure 4. Proposed mechanism for α-enaminone formation.

The scope of the α-enaminone formation reaction was examined using the optimized conditions (Table 2). Arylamines with different substituents at positions 3 and/or 4 were able to give α-enaminones in moderate to good yields (42−64%). We noticed that the reaction appeared to be clean on TLC. However, the yields were not as high as expected. Analysis of this reaction indicates that polymerization of arylamines likely accounts for the lower yields of this reaction, although decomposition of enaminone was not apparent on TLC and the silica column as both decomposition products (cyclohexanone and arylamine) are not easily visible on silica. Given the nature of enaminone, decomposition of enaminone likely happens on the silica column and could contribute to the lower yield of enaminone. The structure of **3i** was confirmed via X-ray crystallography (CCDC 2062654).

Detection of Enamine Formation. The proposed mechanism indicates that enamine is formed in this process. We speculate that enamine intermediate **A** could possibly be detected as it is expected to be more stable than its aliphatic counterpart due to its cross-conjugation to the aryl ring. We decided to track the reaction with ^{1}H NMR spectroscopy in the presence of 10 mol % triflic acid. When cyclohexanone was mixed with *p*-methoxyaniline in $CDCl_3$ in the presence of triflic acid, a triplet at 6.07 ppm corresponding to enaminone-H^b appeared on the spectra. However, the proton shift for enamine-H^a, which is expected to be upfield of enaminone-H^b, was not observed (Figure 5a). We then added TEMPO to see what would happen. To our delight, a weak triplet at 5.80 ppm became visible (Figure 5b), suggesting the possible existence of enamine. This result was counterintuitive as TEMPO was proved to quench this reaction in our earlier experiments. We speculate that when enamine (**A**) was formed, it could quickly react with the arylamine radical generated through SET; as a result, enamine formation was not detected in the absence of TEMPO. When TEMPO was added, the arylamine radical was quenched, slowing the oxidation process, and thus, the enamine could then exist for a longer time to be detectable through NMR spectroscopy. To further prove our speculation, we used another radical scavenger, ascorbic acid. As it turned out, enamine formation was more pronounced in the presence of ascorbic acid (Figure 5c). Using a different solvent, i.e., toluene-d_8, in the presence of TEMPO, these two protons (H^a and H^b) appeared at 5.60 and 5.63 ppm, respectively (Figure 5d). To further confirm the formation of enamine, we carried out COSY and HSQC NMR experiments. The COSY NMR spectrum (Figure 6, left) shows the enamine-H^a peak at 5.80 ppm is coupled to a peak(s) at 2.25 ppm, which is expected for proton shifts of allylic Hs. The HSQC spectrum displays a correlation of the peak at 5.80 ppm with a peak at 106.48 ppm, which is expected for ^{13}C shift of a sp^2 C. Parallel correlations were observed for α-enaminone-H^b: the proton shift at 6.07 ppm exhibits coupling with a peak at 2.32 ppm on the COSY spectrum and correlation with a peak at 112.28 ppm on the HSQC spectrum. It is notable that all of the ^{1}H and ^{13}C shifts of α-enaminone mentioned above are downfield-shifted relative to those of the corresponding enamine, which perfectly matches what is expected for the electron-withdrawing effect of the carbonyl group in enaminone. These NMR spectroscopic

https://doi.org/10.1021/acs.joc.1c01462
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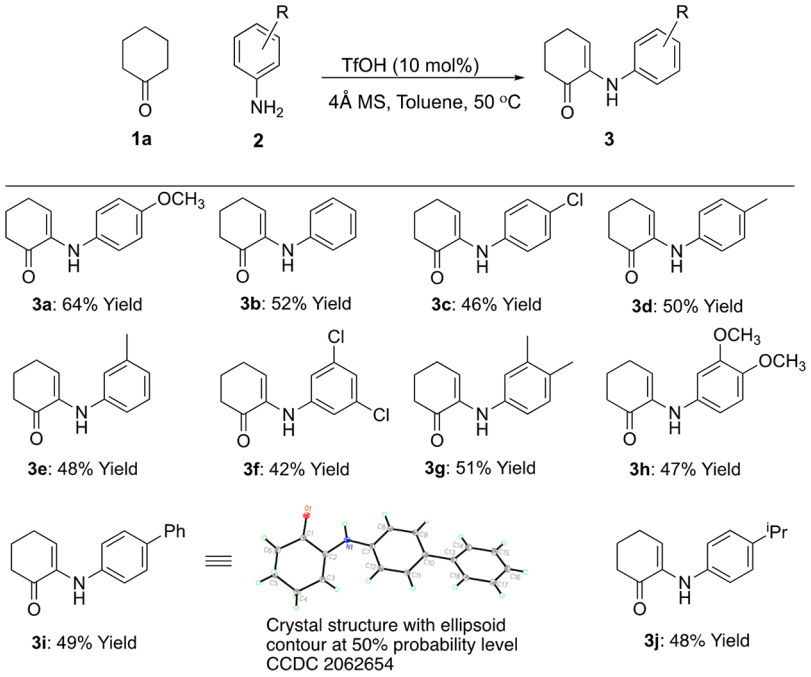
Table 2. Substrate Scope of α-Enaminones[a]



[a]All reactions were carried out with **1a** (4.0 mmol), **2** (0.2 mmol), 4 Å MS (28 mg), and TfOH (10 mol %) in toluene (1.0 mL) at 50 °C for 22−24 h. Isolated yields.

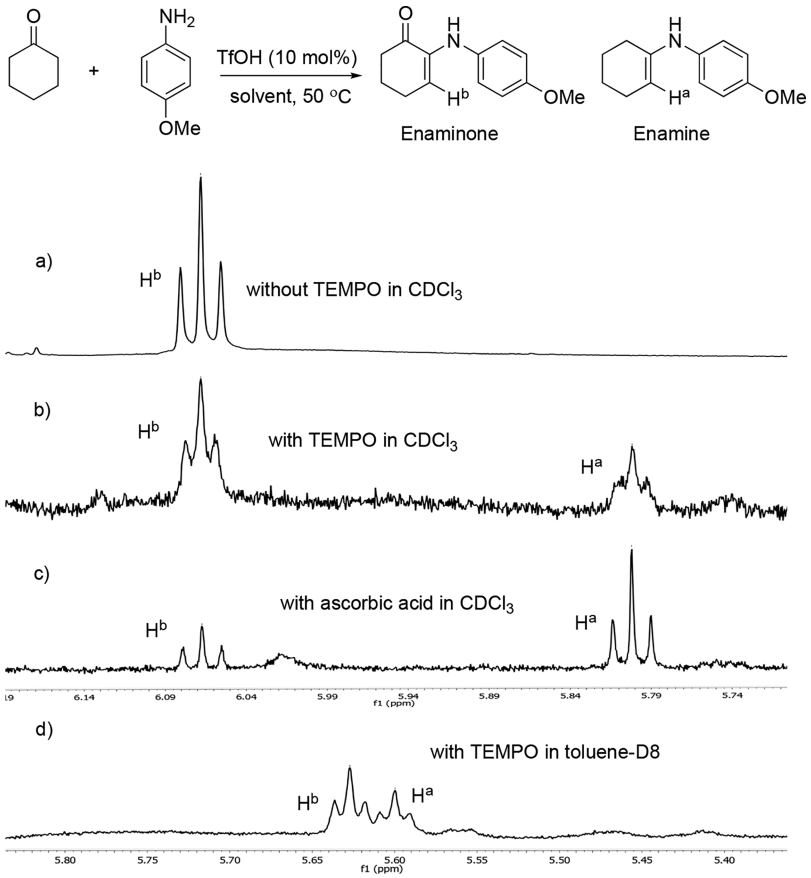


Figure 5. Reactions tracked via ^{1}H NMR spectroscopy in $CDCl_3$. (a) TEMPO was not included. (b) TEMPO was included. (c) Ascorbic acid was included. (d) TEMPO was included in toluene-d_8.

data prove the existence of enamine generated from 1° arylamine and cyclic ketone.

[3+3] Cycloaddition Reaction of α-Enaminone. Having established a concise and versatile method for accessing α-

https://doi.org/10.1021/acs.joc.1c01462
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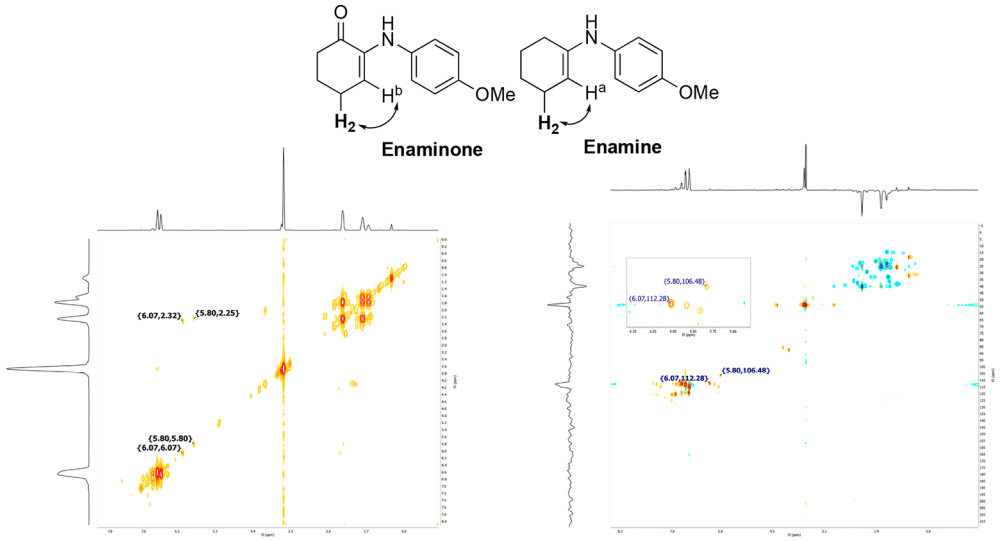
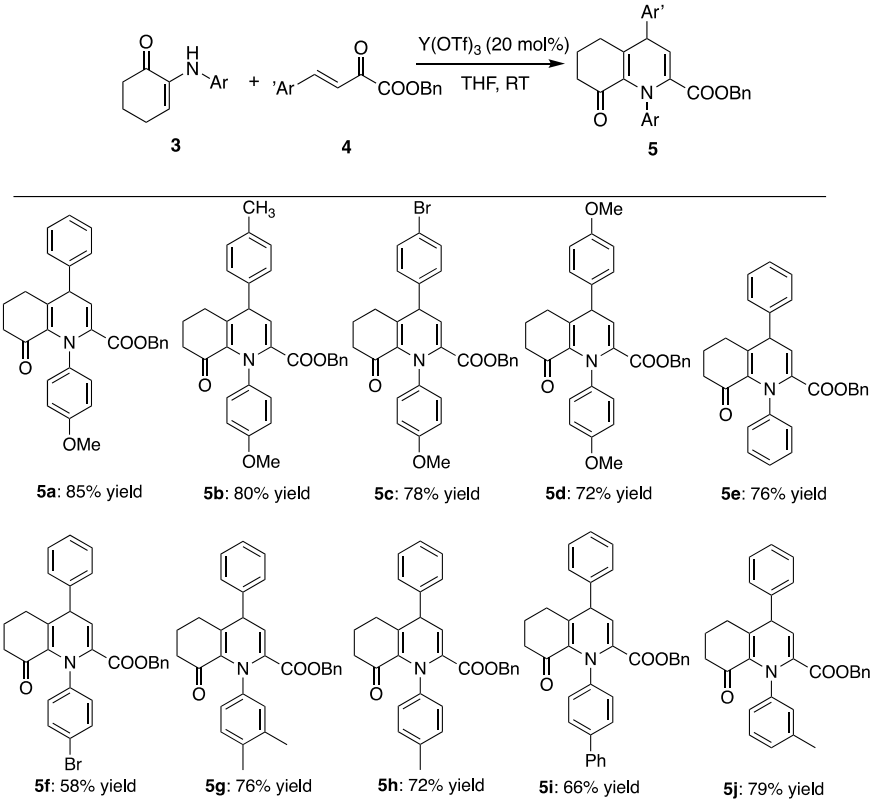


Figure 6. Two-dimensional NMR spectroscopy of the reaction mixture in Figure 5b: (left) COSY NMR and (right) HSQC NMR.

Table 3. [3+3] Cycloaddition Reaction of α-Enaminones and Enones[a]



[a]All reactions were carried out with **3** (0.1 mmol), **4** (0.2 mmol), and $Y(OTf)_3$ (20 mol %) in THF (2.0 mL) at room temperature for 16 h. Isolated yields.

enaminones, we turned our attention to the reactivity of α-enaminones. In a previous work, we developed a three-component aza-Diels–Alder reaction (ADAR) through cooperative enamine–metal Lewis acid catalysis involving an enamine intermediate formed from 1° arylamines.[19] The reactivity and activities of α-enaminones are supposedly different from those of enamine. It would be interesting to determine if a similar reaction could happen to α-enaminones. Aza-Diels–Alder reactions lead to nitrogen-containing heterocycles, which constitute one of the most important structural motifs in natural products, pharmaceuticals, and biosystems.[27,46−51] Incorporation of α-enaminones into ADARs would introduce an extra carbonyl group into the resulting heterocycles, opening new functionalization opportunities.

When α-enaminone (**3a**) was treated with enone (**4a**) in the presence of 20 mol % $Y(OTf)_3$ in THF, a new product (**5a**) was obtained in 54% yield in 4 h (see Table S2, entry 1), suggesting that α-enaminone is active enough for this reaction. The identity of **5a** was revealed as a dihydropyridine and was confirmed with NMR spectroscopy, including ^1H, ^{13}C, COSY,

https://doi.org/10.1021/acs.joc.1c01462
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and HSQC (see the Supporting Information). We also attempted other rare earth metals such as $Yb(OTf)_3$, $La(OTf)_3$, and $Sc(OTf)_3$, however, resulting in much lower yields of **5a** (entries 2−4, respectively). Brønsted acid TfOH and transition metal $Zn(OTf)_2$ gave only traces of the product (entries 5 and 6, respectively). The utilization of an oxidizing $Fe(OTf)_3$ or reducing $Fe(OTf)_2$ did not improve the yield (entries 7 and 8) either. We decided to change the **3a**/**4a** molar ratio to see if it would make a difference. While a **3a**/**4a** molar ratio of 1/2 increased the yield of **5a** to 73% (entry 9), the reverse ratio of 2/1 decreased the yield to 52% (entry 11). Placing the reaction mixture under argon further increased the yield to 85% (entry 10). Decreasing the catalyst loading to 10 mol % deactivated the reaction (entry 15). Shortening the reaction time from 16 to 4 h also decreased the yield of **5a** (69%, entry 16). Both higher and lower temperatures had adverse effects on the reaction (entries 12−14). We also screened the reaction in different solvents (entries 17−22). THF turned out to be the best solvent for this reaction.

Using the optimized condition (see Table S2, entry 10), the reaction scope was explored (Table 3). α-Enaminones with electron-donating groups at position 3 or 4 of the aniline ring generated the products in good yields (**5a** and **5g**−**5j**, 66−85%). α-Enaminone with a slightly electron-withdrawing bromo group at position 4 of the aniline also worked, giving a moderate yield (**5f**, 58%). On the contrary, enones with an electron-donating group at position 4 led to the products in good yields (**5a**, **5b**, **5d**, and **5e**). Enone with a slightly electron-withdrawing *p*-bromophenyl group at position 4 produced dihydropyridines in good yield (**5c**, 78%).

The mechanism of this reaction is proposed (Figure 7). α-Enaminone serves as an enamine nucleophile to add to the

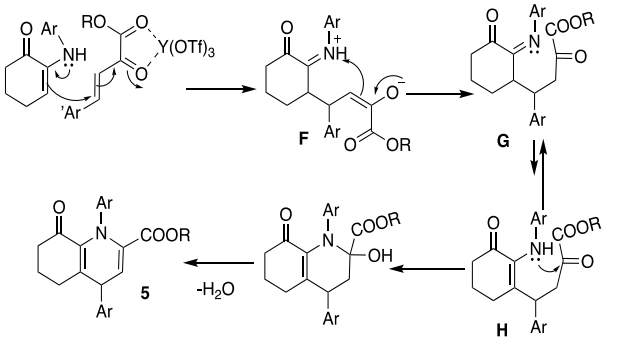

Figure 7. Proposed mechanism of the [3+3] cycloaddition reaction.

enone Michael acceptor activated by $Y(OTf)_3$, forming intermediate **F**, which upon intramolecular proton transfer affords imine intermediate **G**. Intermediate **G** undergoes N-tautomerization to generate enamine intermediate **H**. Addition of amine to the carbonyl group followed by dehydroxylation leads to product **5**. Notably, this mechanism indicates a [3+3] cycloaddition reaction of enaminone and enone, which is different from the mechanism of the aza-HDA reaction of ketone and enones through cooperative enamine−metal Lewis acid catalysis reported by us previously.[19] The [3+3] cycloaddition reaction involves a key N-tautomerization step, whereas the aza-HDA reaction proceeded with a cascade sequence. It is apparent that α-enaminone possesses a set of reactivities different from that of enamine.

CONCLUSIONS

Primary amines directly form imines with aldehydes/ketones. Although theoretically imines can isomerize into enamine, the existence of enamine through isomerization of imines has never been proved with experimental evidence. In this work, we prove for the first time that enamine can be formed from 1° arylamine using a metal Lewis acid or a Brønsted acid as the catalyst. The formation of enamine was detected when a radical quencher such as TEMPO or ascorbic acid was added to the mixture for the reaction of cyclic ketone with 1° arylamine. The identity of the enamine was confirmed via NMR spectroscopy, including ^{1}H NMR, COSY, and HSQC NMR spectroscopy. Given the important role enamine chemistry plays in organic chemistry and chemical catalysis, the knowledge and information gained about the formation of enamine will advance our basic understanding of organic chemistry, expand the scope of enamine chemistry, and facilitate further exploration of enamine in catalysis and synthesis.

A new method has been developed for the direct formation of enaminone from 1° arylamines and cyclic ketones, offering a concise and convenient access to enaminones. A radical quencher such as TEMPO or ascorbic acid was found to retard enaminone formation, which is in sharp contrast with the previous work in which TEMPO served as an O_2 carrier. These data reflect the complex and multifunctional nature of α-enaminones, elucidating the potential of α-enaminone as a new type of substrate. In addition, a new [3+3] cycloaddition reaction of α-enaminones and enones was developed, leading to dihydropyridines in good yields. α-Enaminones displayed a new set of reactivities acting as both enamine and nitrogen nucleophiles. The investigation of α-enaminones will open the door to designing new reaction patterns and offers the opportunity to develop a large number of new reactions. The exploration of the reactivity and reaction modes of α-enaminones in other reactions is underway in our laboratory.

EXPERIMENTAL SECTION

General Experimental Information. ^{1}H NMR spectra were recorded on commercial instruments (400 or 500 MHz). Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26). Spectra are reported as follows: chemical shift (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (hertz), integration, and assignment. ^{13}C NMR spectra were recorded on commercial instruments (101 or 126 MHz) with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ 77.0). ESI-HRMS spectra were recorded using a commercial apparatus, and chloroform was used to dissolve the sample. X-ray crystallographic data were collected using a SMART APEX II diffractometer. Unless otherwise indicated, reagents obtained from commercial sources were used without further purification. Solvents were dried and distilled prior to use according to the standard methods. Arylamine **2** were purchased from either Acros Organics or Sigma-Aldrich. All enones **4** and α-enaminones (when required in bulk) were prepared using the methods described previously.[52−54]

General Procedure for the Preparation of α-Enaminones. In an oven-dried reaction tube, cyclohexanone **1** (4.0 mmol) was dissolved in anhydrous toluene (1.0 mL). To this solution were added trifluoromethanesulfonic acid (TfOH, 10 mol %), arylamine **2** (0.2 mmol), and 4 Å molecular sieves (28 mg). The reaction mixture was stirred for 22−24 h (monitored by TLC) at 50 °C in an oil bath with molecular oxygen bubbling through the reaction mixture (2−3 O_2

https://doi.org/10.1021/acs.joc.1c01462
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bubbles per second). The resulting mixture was purified via silica gel column chromatography (9/1 hexane/EtOAc) to afford the pure products **3a−j**. **3a−3e** and **3i** are characterized in ref 32.

*2-[(3,5-Dichlorophenyl)amino]cyclohex-2-en-1-one (**3f**).* The title compound was synthesized according to the general procedure on a 0.2 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **3e** (21.5 mg, 42% yield): yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, J = 1.8 Hz, 2H), 6.86 (t, J = 1.8 Hz, 1H), 6.49 (t, J = 4.7 Hz, 1H), 6.46 (s, 1H), 2.60−2.55 (m, 2H), 2.52 (dd, J = 10.9, 5.9 Hz, 2H), 2.07−2.02 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 195.1, 144.1, 135.4, 135.0, 120.4, 120.13, 115.6, 37.5, 24.6, 22.6; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{12}H_{12}Cl_2NO$ 256.2096, found 256.2090.

*2-[(3,4-Dimethylphenyl)amino]cyclohex-2-en-1-one (**3g**).* The title compound was synthesized according to the general procedure on a 0.2 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **3g** (22 mg, 51% yield): yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 7.9 Hz, 1H), 6.88−6.75 (m, 2H), 6.32 (t, J = 4.7 Hz, 1H), 6.21 (s, 1H), 2.61−2.51 (m, 2H), 2.43 (dd, J = 11.0, 5.6 Hz, 2H), 2.23 (s, 3H), 2.20 (s, 3H), 2.01 (dt, J = 12.4, 6.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 195.7, 139.6, 137.4, 136.8, 130.2, 129.6, 121.0, 116.8, 115.2, 37.8, 24.6, 23.0, 20.0, 19.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{14}H_{17}NO$ 216.1388, found 216.1384.

*2-[(3,4-Dimethoxyphenyl)amino]cyclohex-2-en-1-one (**3h**).* The title compound was synthesized according to the general procedure on a 0.2 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **3h** (23.3 mg, 47% yield): yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, J = 8.3 Hz, 1H), 6.63 (dt, J = 4.2, 2.4 Hz, 2H), 6.21 (t, J = 4.8 Hz, 1H), 6.14 (s, 1H), 3.86 (s, 6H), 2.57 (t, 2H), 2.43 (dd, J = 11.1, 5.7 Hz, 2H), 2.06−1.99 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 195.6, 149.5, 144.4, 137.6, 135.4, 114.5, 112.1, 112.0, 105.7, 56.2, 55.9, 37.8, 24.5, 23.1; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{14}H_{18}NO_3$ 248.1287, found 248.1280.

*2-[(4-Isopropylphenyl)amino]cyclohex-2-en-1-one (**3j**).* The title compound was synthesized according to the general procedure on a 0.2 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **3j** (22.1 mg, 48% yield): yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.2 Hz, 2H), 6.98 (d, J = 8.2 Hz, 2H), 6.35 (t, J = 4.6 Hz, 1H), 6.28 (s, 1H), 2.93−2.79 (m, 1H), 2.61−2.50 (m, 2H), 2.43 (dd, J = 10.7, 5.4 Hz, 2H), 2.01 (dt, J = 12.3, 6.0 Hz, 2H), 1.24 (s, 3H), 1.23 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 195.6, 141.9, 139.6, 136.7, 127.1, 119.2, 115.4, 37.8, 33.4, 24.6, 24.1, 23.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{15}H_{19}NO$ 230.1545, found 230.1542.

General Procedure for the Preparation of [3+3] Cycloaddition Products (5a−j). In an oven-dried reaction vial, α-enaminone **3** (0.1 mmol), enone **4** (0.2 mmol), and Y(OTf)$_3$ were combined, and the vial was flushed with argon three times. Under inert atmospheric conditions, anhydrous THF (2.0 mL) was added to the vial and the resulting reaction mixture was stirred at room temperature until the reaction had reached completion (monitored by TLC). The reaction mixture was then purified via silica gel column chromatography (9/1 hexane/EtOAc or 5/0.5/1 hexane/DCM/acetone) to afford the pure products **5a−j**.

*Benzyl 1-(4-Methoxyphenyl)-8-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5a**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **5a** (39.6 mg, 85% yield): yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.30 (m, 10H), 7.07−7.05 (m, 2H), 6.65 (d, J = 10.0 Hz, 2H), 5.85 (d, J = 9.0 Hz, 2H), 4.93 (dd, J = 10, 35 Hz) 3.29 (d, J = 10.0 Hz, 1H), 3.69 (s, 3H), 2.27−2.22 (m, 2H), 2.13−2.06 (m, 2H), 1.85−1.73 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.4, 164.1, 158.0, 142.5, 138.2, 137.7, 137.5, 137.2, 136.8, 135.4, 131.1, 129.1, 128.4, 128.4, 128.1, 127.5, 116.0, 113.0, 66.7, 55.3, 46.0, 39.0, 29.2, 22.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{30}H_{27}NO_4$ 466.2018, found 466.2012.

*Benzyl 1-(4-Methoxyphenyl)-8-oxo-4-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5b**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **5b** (38.4 mg, 80% yield): yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 9.0 Hz, 2H), 7.31−7.20 (m, 7H), 7.17−7.12 (m, 2H), 6.74 (d, J = 9.0 Hz, 2H), 5.93 (d, J = 4.6 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 4.96 (d, J = 12.3 Hz, 1H), 4.33 (d, J = 4.6 Hz, 1H), 3.78 (s, 3H), 2.39 (s, 3H), 2.37−2.30 (m, 2H), 2.30−2.10 (m, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.5, 164.1, 158.0, 139.6, 138.3, 137.6, 137.5, 137.2, 136.7, 135.4, 131.1, 129.7, 128.4, 128.2, 128.1, 116.3, 113.0, 66.7, 55.3, 45.6, 39.0, 29.2, 22.0, 21.1; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{31}H_{29}NO_4$ 480.2175, found 480.2188.

*Benzyl 4-(4-Bromophenyl)-1-(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5c**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **5c** (42.4 mg, 78% yield): pale yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.9 Hz, 2H), 7.28 (m, 2H), 7.17−7.11 (m, 2H), 6.73 (d, J = 8.9 Hz, 2H), 5.85 (d, J = 4.6 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 4.97 (d, J = 12.3 Hz, 1H), 4.34 (d, J = 4.6 Hz, 1H), 3.78 (s, 3H), 2.44−2.26 (m, 2H), 2.26−2.11 (m, J = 10.2, 5.3 Hz, 2H), 1.94−1.81 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.3, 163.9, 158.1, 141.6, 137.9, 137.7, 137.2, 136.2, 135.3, 132.2, 131.0, 130.0, 128.4, 128.2, 121.4, 114.9, 113.1, 66.8, 55.3, 45.5, 39.0, 29.1, 22.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{30}H_{26}BrNO_4$ 544.1123, found 544.1117.

*Benzyl 1,4-Bis(4-methoxyphenyl)-8-oxo-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5d**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **5d** (35.7 mg, 72% yield): yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2H), 7.32−7.23 (m, J = 8.2, 3.4, 2.1 Hz, 5H), 7.17−7.10 (m, 2H), 6.94 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.90 (d, J = 4.5 Hz, 1H), 5.04 (d, J = 12.3 Hz, 1H), 4.95 (d, J = 12.3 Hz, 1H), 4.30 (d, J = 4.6 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 2.34−2.27 (m, 2H), 2.21−2.09 (m, 2H), 1.92−1.79 (m, J = 18.7, 10.4, 5.8 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.4, 164.1, 158.9, 158.0, 138.3, 137.6, 137.5, 136.7, 135.4, 134.7, 131.0, 129.4, 128.4, 128.3, 128.1, 116.2, 114.4, 113.0, 66.7, 55.3, 55.2, 45.1, 39.0, 29.1, 22.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{31}H_{29}NO_5$ 496.2124, found 496.2130.

*Benzyl 8-Oxo-1,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5e**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (5/0.5/1 hexane/DCM/acetone) to afford **5e** (33.2 mg, 76% yield): yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.10 (m, 15H), 5.99 (d, J = 4.7 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1H), 4.97 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 4.7 Hz, 1H), 2.37−2.30 (m, 2H), 2.25−2.14 (m, 2H), 1.95−1.83 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.3, 164.0, 145.6, 142.3, 138.1, 137.8, 136.8, 135.3, 129.5, 129.1, 128.4, 128.4, 128.3, 128.2, 128.1, 127.5, 126.7, 116.9, 66.8, 46.1, 38.9, 29.2, 22.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{29}H_{25}NO_3$ 436.1913, found 436.1918.

*Benzyl 1-(4-Bromophenyl)-8-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5f**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (5/0.5/1 hexane/DCM/acetone) to afford **5f** (29.8 mg, 58% yield): yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.25 (m, 12H), 7.15−7.09 (m, 1H), 6.94 (d, J = 8.9 Hz, 1H), 6.02 (d, J = 4.7 Hz, 1H), 5.07 (d, J = 12.2 Hz, 1H), 4.96 (d, J = 12.2 Hz, 1H), 4.35 (d, J = 4.7 Hz, 1H), 2.40−2.28 (m, 2H), 2.25−2.14 (m, 2H), 1.96−1.80 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.2, 163.7, 144.7, 142.0, 138.8, 137.4, 136.3, 135.2, 131.3, 131.2, 129.1, 129.1, 129.0, 128.9, 128.7, 128.4, 128.4, 128.3, 128.3, 127.6, 126.8, 120.4, 117.6, 66.9, 46.0, 38.9, 29.7, 29.2, 21.9; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{29}H_{24}BrNO_3$ 514.1018, found 514.1031.

https://doi.org/10.1021/acs.joc.1c01462
J. Org. Chem. 2021, 86, 14617−14626

*Benzyl 1-(3,4-Dimethylphenyl)-8-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5g**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (9/1 hexane/EtOAc) to afford **5g** (35.3 mg, 76% yield): yellow syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.29 (m, 6H), 7.28−7.26 (m, J = 1.7 Hz, 1H), 7.25−7.20 (m, 2H), 7.14−7.09 (m, 2H), 6.98 (d, J = 7.1 Hz, 1H), 5.96−5.92 (m, J = 4.7 Hz, 1H), 5.06 (dd, J = 9.8, 4.8 Hz, 1H), 4.95 (d, J = 12.3 Hz, 1H), 4.36 (d, J = 4.7 Hz, 1H), 2.36−2.29 (m, 2H), 2.22−2.13 (m, 9H), 1.91−1.82 (m, J = 12.4, 9.4, 3.7 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.4, 164.2, 143.2, 142.4, 137.8, 137.7, 137.0, 136.1, 135.4, 135.0, 130.4, 129.2, 129.0, 128.7, 128.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.4, 127.0, 116.3, 66.7, 46.0, 39.0, 31.6, 29.2, 22.7, 22.0, 19.8, 19.4, 14.1; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{31}H_{29}NO_3$ 464.2226, found 464.2231.

*Benzyl 8-Oxo-4-phenyl-1-(p-tolyl)-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5h**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (5/0.5/1 hexane/DCM/acetone) to afford **5h** (32.4 mg, 72% yield): yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.37 (m, 1H), 7.35−7.30 (m, 1H), 7.28 (dd, J = 5.0, 1.8 Hz, 1H), 7.14 (dd, J = 6.3, 3.3 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 5.95 (d, J = 4.7 Hz, 1H), 5.06 (d, J = 12.3 Hz, 1H), 4.96 (d, J = 12.3 Hz, 1H), 4.37 (d, J = 4.6 Hz, 1H), 2.33 (dd, J = 8.0, 4.4 Hz, 1H), 2.31 (s, 1H), 2.21−2.15 (m, 1H), 1.92−1.83 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.4, 164.1, 143.0, 142.4, 137.7, 137.6, 136.9, 136.4, 135.4, 129.4, 129.04, 128.7, 128.4, 128.3, 128.1, 127.5, 116.3, 66.7, 46.1, 39.0, 29.2, 22.0, 21.1; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{30}H_{27}NO_3$ 450.2069, found 450.2055.

*Benzyl 1-[(1,1′-Biphenyl)-4-yl]-8-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5i**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (5/0.5/1 hexane/DCM/acetone) to afford **5i** (33.8 mg, 66% yield): pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, J = 1.7 Hz, 1H), 7.54−7.52 (m, 1H), 7.52−7.50 (m, 1H), 7.45−7.30 (m, 11H), 7.25−7.21 (m, 3H), 7.15−7.10 (m, 2H), 6.03 (d, J = 4.7 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 4.98 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 4.7 Hz, 1H), 2.39−2.33 (m, 2H), 2.26−2.16 (m, 2H), 1.90 (ddd, J = 18.7, 10.1, 5.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.4, 169.9, 164.0, 142.1, 140.6, 139.2, 136.9, 134.3, 133.5, 133.5, 129.6, 129.1, 128.7, 128.4, 128.3, 128.1, 127.5, 127.2, 127.0, 126.7, 117.3, 97.0, 66.9, 46.1, 38.9, 29.2, 22.0; HRMS (ESI) m/z [M + H$^+$] calcd for $C_{35}H_{29}NO_3$ 512.2226, found 512.2234.

*Benzyl 8-Oxo-4-phenyl-1-(m-tolyl)-1,4,5,6,7,8-hexahydroquinoline-2-carboxylate (**5j**).* The title compound was synthesized according to the general procedure on a 0.1 mmol scale and purified using silica gel column chromatography (5/0.5/1 hexane/DCM/acetone) to afford **5j** (35.6 mg, 79% yield): yellow syrup; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.34 (m, 3H), 7.32−7.29 (m, 5H), 7.22 (d, 2H), 7.06 (t, J = 7.8 Hz, 1H), 6.81 (dd, J = 15.5, 7.5 Hz, 2H), 6.69 (d, J = 7.4 Hz, 1H), 6.18 (d, J = 2.5 Hz, 1H), 5.29 (d, J = 12.6 Hz, 1H), 5.13 (d, J = 12.6 Hz, 1H), 4.55 (s, 1H), 3.47 (dd, J = 11.3, 2.5 Hz, 1H), 2.75 (td, J = 13.5, 6.2 Hz, 1H), 2.33−2.27 (m, 2H), 2.24 (s, 3H), 2.20−2.14 (m, 1H), 2.06−1.98 (m, 1H); ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 205.3, 162.5, 142.3, 141.4, 140.5, 139.2, 135.6, 129.3, 129.0, 128.4, 128.3, 128.0, 127.8, 127.7, 121.6, 117.2, 114.2, 113.6, 90.2, 66.7, 50.0, 42.4, 38.7, 26.6, 26.3, 21.5.

[3+3] Cycloaddition on a Larger Scale. 2-(Phenylamino)-cyclohex-2-en-1-one **3b** (93.6 mg, 0.5 mmol), benzyl (*E*)-2-oxo-4-phenylbut-3-enoate **4e** (266.3 mg, 1.0 mmol), and Y(OTf)$_3$ (53.6 mg, 0.1 mmol) were mixed in a round-bottom flask and stirred in THF (5 mL) at room temperature for 16 h. The reaction was then stopped, and the reaction mixture was purified on a silica column (5/1/0.5 hexane/acetone/DCM) to afford 75.4 mg of **5e** in 35% yield.

α-Enaminone Formation on a Larger Scale. Cyclohexanone **1** (40.0 mmol, 4.1 mL) was dissolved in anhydrous toluene (10 mL) in a round-bottom flask. To this solution were added trifluoromethanesulfonic acid (TfOH, 10 mol %, 18 μL), arylamine **2a** (2.0 mmol, 246.1 mg), and molecular sieves (280 mg, 4 Å). The reaction mixture was stirred for 24 h at 50 °C in an oil bath with molecular oxygen bubbling through the reaction mixture. The reaction mixture was purified on a silica column (9/1 hexane/EtOAc) to afford the pure product **3a** (106.5 mg, 49% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01462.

Experimental procedures; ^{1}H NMR, ^{13}C NMR, and other characterization data; and single-crystal X-ray analysis (PDF)

Accession Codes

CCDC 2062654 contains 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

The authors declare no competing financial interest.

[§]Deceased April 2021.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant CHE-1954422. The authors acknowledge the National Science Foundation MRI Program (CHE-1726652) and the University of North Texas for supporting the acquisition of the Rigaku XtaLAB Synergy-S X-ray diffractometer. The authors thank Dr. Guido Verbeck and the Laboratory for Imaging Mass Spectrometry at the University of North Texas for mass spectrometry data.

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