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Three Component Cascade Reaction of Cyclohexanones, Aryl Amines, and Benzoylmethylene Malonates: Cooperative Enamine-Brønsted Acid Approach to Tetrahydroindoles

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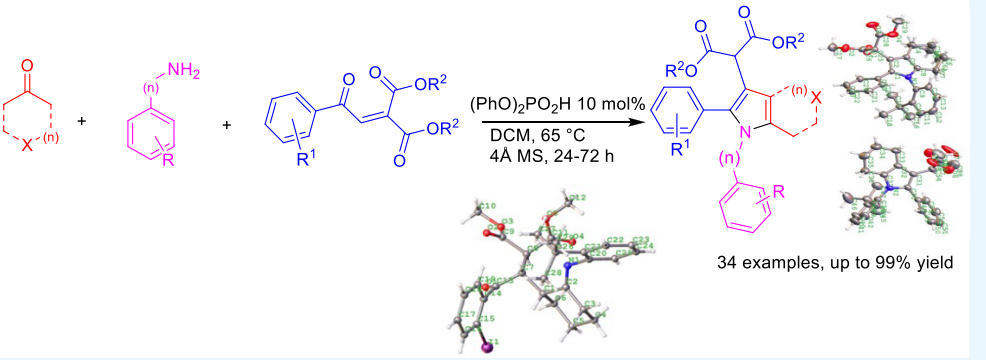

ABSTRACT: A three-component cascade reaction comprising cyclic ketones, arylamines, and benzoylmethylene malonates has been developed to access 4,5,6,7-tetrahydro-1*H*-indoles. The reaction was achieved through cooperative enamine-Brønsted catalysis in high yields with wide substrate scopes. Mechanistic studies identified the role of the Brønsted acid catalyst and revealed the formation of an imine intermediate, which was confirmed by X-ray crystallography.

1. INTRODUCTION

Nitrogen-containing heterocycles are essential components of a wide range of bioactive natural products.[1] Nitrogen-based heterocycles have exhibited a wide range of biological activities including cancer, HIV, diabetes, tuberculosis, and Alzheimer's disease.[2] 4,5,6,7-Tetrahydro-1*H*-indoles represent an important class of structural scaffolds in the design and derivation of new pharmacophores, which can act as inhibitors for tyrosine kinase,[3] anti-hepatitis C virus,[4] anti-cancer and anti-oxidant agents,[5] and natural products.[6] 4,5,6,7-Tetrahydro-1*H*-indoles also serve as synthetic intermediates for natural products such as goniomitine[7] and chuangxinmycin.[8] Recently, 4,5,6,7-tetrahydro-1*H*-indoles have also been found to be present in sponge Scalarispongia species.[9]

Considerable efforts have been devoted to developing synthetic methods to construct 4,5,6,7-tetrahydro-1*H*-indoles due to their diverse biological activity. Syntheses of N-substituted 4,5,6,7-tetrahydro-1*H*-indoles have been achieved through metal Lewis acid catalysis,[10] Brønsted acid catalysis,[11] and microwave synthesis.[12] Catalyst-free conditions have also been reported.[13] Benzoylmethylene malonates are effective Michael acceptors[14] and have been utilized for the synthesis of heterocycles including furans, quinoxalines, imidazoles, benzo-[1,4]-thiazines, 2,4,5-trisubstituted oxazole, and pyrroloben-zoxazines.[15] In 2016, Jia and coworkers reported Friedel−Crafts reactions with benzoylmethylene malonates to afford enantioselective Michael products using $Cu(OTf)_2$ and (*S*)-*i*Pr-bisoxazoline as the catalyst (Figure 1a).[16] Kakiuchi et al. developed an efficient cyclization reaction with benzoylmethylene malonates and propargyl alcohols for the synthesis of hydrofurans (Figure 1b).[17] Bisht and Peddinti reported a $FeCl_3$ mediated reaction of preformed *β*-enamino ester and benzoylmethylene malonates affording pyrrolobenzoxazines (Figure 1c).[18]

It has been reported that the reaction of activated alkenes[18,19] or 2,3-diketoesters[20] with aldehydes/ketones and amines can afford pyrroles or hydroxyindoles. Most of these reactions are through the *β*-enaminone intermediate, which is derived from a 1,3-diketone and an amine. *β*-Enaminone is a common synthetic intermediate/substrate for the synthesis of pyrrole.[21] In contrast, there are only three reports in the

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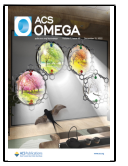

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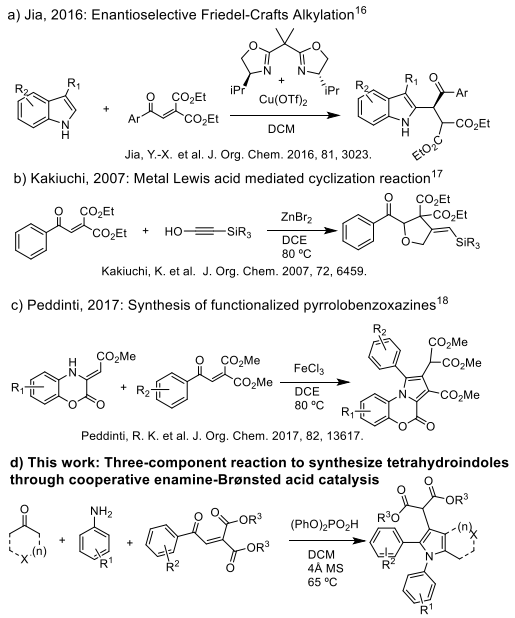


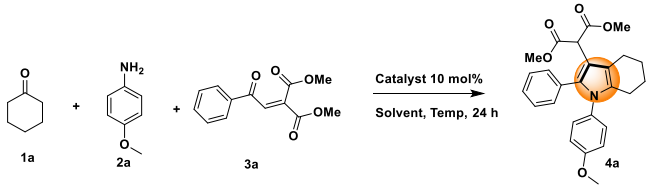
Figure 1. Reactions developed with benzoylmethylene malonates for heterocyclic compounds. (a) Jia et al., 2016.[16] (b) Kakiuchi et al., 2007.[17] (c) Bisht and Peddinti, 2017.[18] (d) This work.

literature likely going through enamine intermediate to construct pyrroles, two of which utilized nitroalkene as the enamine acceptor[12, 19d] and the other one utilized 3-nitrobenzo[*b*]thiophene as the enamine acceptor.[19e] We became interested in utilizing benzoylmethylene malonates to develop a new synthetic method for tetrahydroindoles/pyrroles through cooperative enamine-metal Lewis acid/Brønsted acid catalysis (Figure 1d). Very recently, our group has demonstrated the feasibility of arylamines serving as effective catalysts in enamine synthesis leveraging a reversed soft−hard strategy.[22] The development of a new method to access tetrahydroindoles/pyrroles through enamine and benzoylmethylene malonates will extend the utility of enamine, providing a convenient approach to this important class of compounds not available with existing methods.

2. RESULTS AND DISCUSSION

We started our investigation with cyclohexanone (**1a**), 4-methoxyaniline (**2a**) and dimethyl 2-(2-oxo-2-phenylethylidene) malonate (**3a**) (Table 1). Metal Lewis acids including $Sc(OTf)_3$, $Cu(OTf)_2$, and $Y(OTf)_3$ were first assessed to catalyze this reaction in toluene at 50 °C. We were delighted to find out that the desired product (**4a**) was formed in all these reactions. However, the yields were low (18−45%, entries 1−3). The starting materials were mainly recovered after the reactions were worked up. We then tested different solvents using $Y(OTf)_3$ as the catalyst (entries 4−9), which gave the highest yield in toluene (entry 2). Dichloromethane (DCM) turned out to be the best solvent offering **4a** in 61% yield (entry 4). Interestingly, increasing the load of the catalyst by twofold did not increase the yield (entry 9). Addition of 4 Å MS enhanced the yield to 70% (entry 10). Raising the temperature to 60 °C significantly improved the efficiency of the reaction (88%, entry 11). The addition of more 4 Å MS or longer reaction time did not affect the reaction significantly (entries 12 & 13). Addition of a slight excess of 4-methoxyaniline improved the yield to 91% (entry 14).

Table 1. Optimization of Conditions[a]



entry	solvent	catalyst	*T* (°C)	additive (4 Å MS)	yield (%)[b]
1[c]	toluene	$Sc(OTf)_3$	50		18
2[c]	toluene	$Y(OTf)_3$	50		45
3[c]	toluene	$Cu(OTf)_2$	50		10
4[c]	DCM	$Y(OTf)_3$	50		61
5[c]	THF	$Y(OTf)_3$	50		6
6[c]	EtOAc	$Y(OTf)_3$	50		8
7[c]	CH_3CN	$Y(OTf)_3$	50		33
8[c]	$CHCl_3$	$Y(OTf)_3$	50		46
9[d]	DCM	$Y(OTf)_3$	50		50
10	DCM	$Y(OTf)_3$	50	10 mg	70
11	DCM	$Y(OTf)_3$	60	10 mg	88
12	DCM	$Y(OTf)_3$	60	20 mg	85
13[e]	DCM	$Y(OTf)_3$	60	10 mg	87
14[f]	DCM	$Y(OTf)_3$	60	10 mg	91
15[f]	DCM	$Yb(OTf)_3$	60	10 mg	90
16[f]	DCM	$(PhO)_2PO_2H$	60	10 mg	93
17[f]	CCl_4	$(PhO)_2PO_2H$	60	10 mg	87
18[f]	DCM	$(PhO)_2PO_2H$	65	10 mg	96

[a]The reactions were conducted with 1.0 mmol of **1a**, 0.1 mmol of **2a**, and 0.1 mmol of **3a** for 24 h in 1 mL of solvent. [b]Isolated yield. [c]NMR yield. [d]20% of $Y(OTf)_3$ was used. [e]Stirred for 48 h. [f]1.1 eq of 4-methoxyaniline was used.

$Yb(OTf)_3$ (entry 15) showed similar activity with $Y(OTf)_3$. A Brønsted acid, i.e., diphenyl phosphate, was also attempted and turned out to be slightly better than metal Lewis acids (entries 16 & 17). Finally, when the temperature was raised to 65 °C, an excellent yield of 96% yield was achieved (entry 18).

We then investigated the substrate scope of this reaction with different benzoylmethylene malonates (Table 2). Benzoylmethylene malonates with different substituents on the phenyl rings were reacted with cyclohexanone and 4-methoxyaniline under optimal conditions. Both electron-donating and electron-withdrawing groups at meta, ortho, and para positions afforded the desired 4,5,6,7-tetrahydro-1*H*-indoles in high yields (**4b-4i**, 89−99%). Disubstituted aryl groups at the meta-positions including the bulky CF_3 also gave good yields (**4j** and **4k**). However, trisubstituted aryl groups at both para and ortho positions did not give any product, indicating that steric hindrance is at play in this case (**4o**, 0%). We also tried different ester groups of the benzoylmethylene malonates (**4l−4n,** 83−96%). Larger esters such as isopropoxy esters (**4m** and **4n**) also worked well for this reaction.

The substrate scope of arylamine and cyclic ketone were also explored (Table 3). The reaction of *p*-methoxyaniline and **3a** worked smoothly with a 7-membered cyclic ketone, affording the desired 4,5,6,7-tetrahydro-1*H*-indole in 89% yield (**5a**). Five-membered cyclic ketone also reacted with *p*-methoxyaniline and **3a**, albeit giving the product in lower yield (**5b**, 75%), likely due to the higher ring strain upon fusion with the 5-membered pyrrole ring. Six-membered heterocyclic ketones generated the desired products in good yields (**5c** & **5d**, 87 and 83% yield, respectively). Substituted cyclohexanone also

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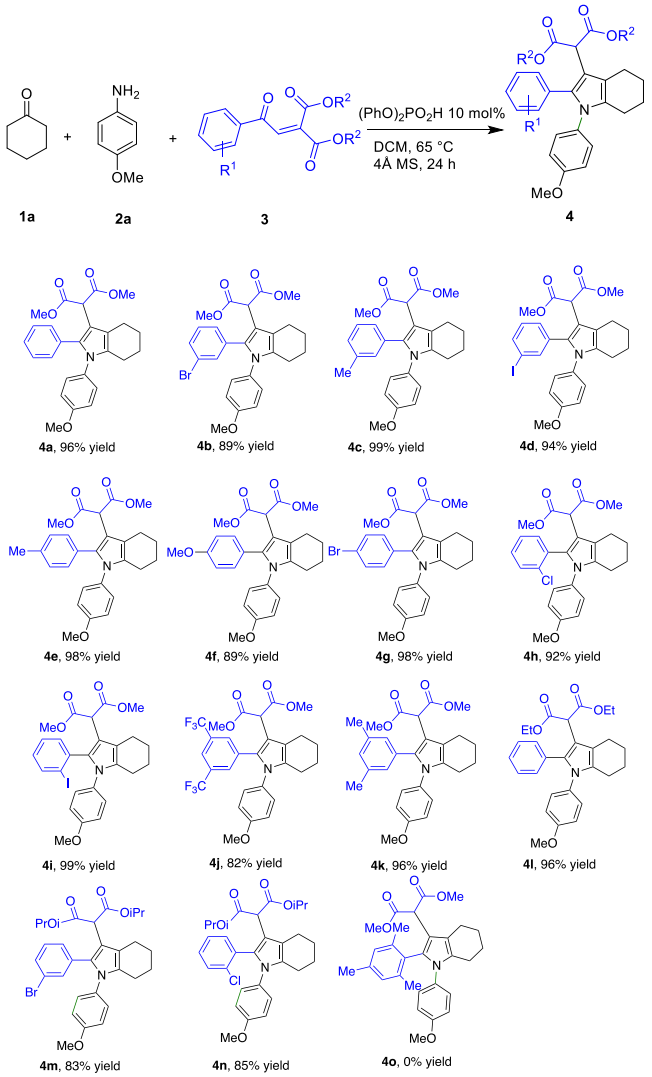
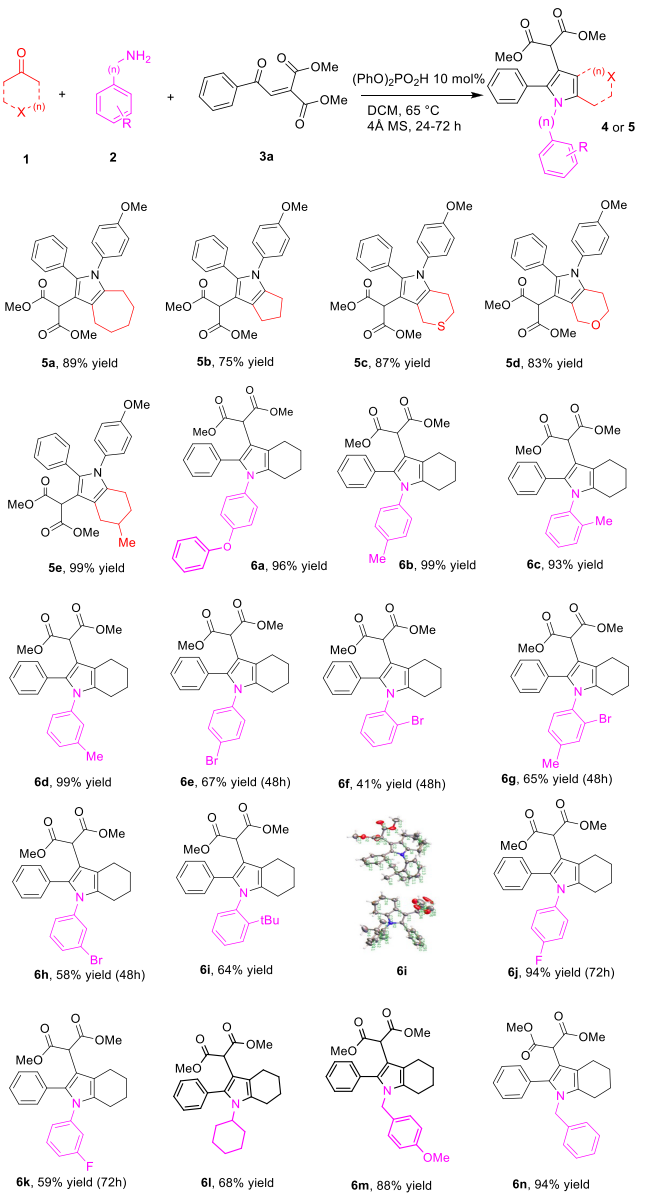
Table 2. Substrate Scope of Benzoylmethylene malonates[a,b]



[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.11 mmol), **3** (0.1 mmol), 4 Å MS (10 mg), DCM (1 mL) at 65 °C for 24 h. [b]Isolated yields.

Table 3. Substrate Scope of Ketone and Arylamine[a,b]



[a]Reaction conditions: **1** (1.0 mmol), **2** (0.11 mmol), **3a** (0.1 mmol), 4 Å MS (10 mg), DCM (1 mL) at 65 °C for 24−72 h. [b]Isolated yields.

produced the product in excellent yield (**5e**, 99% yield). For the scope of arylamine, electron-donating groups including methyl and methoxy groups at ortho, meta, and para positions reacted efficiently with cyclohexanone and **3a**, leading to the formation of the products in good yield in 24 h (**6a**−**6d**, 93−99% yield). When electron-withdrawing bromo was present at the ortho, para, and meta positions of the arylamines, longer reaction times (48 h) were needed and the yields decreased (**6e**−**6h**, 41−67% yield). It is notable that the *o*-bromoaniline gave the lowest yield (41%), possibly due to the proximity of the large substituent and the NH_2 slowing down the formation of enamine with the cyclohexanone. This effect was also observed with **6i** (64% yield), where a bulky *t*-butyl group is placed at the ortho position of the arylamine. In the case of fluoroaniline, it is interesting that the *p*-fluoroaniline was able to generate the product in 94% yield in 72 h. In contrast, *m*-fluoroaniline resulted in the product in only 59% yield in 72 h (**6k**). Strongly electron-withdrawing nitro group at the ortho and para position of the arylamines were also attempted but did not produce the desired product owning to their low nucleophilicity. Aliphatic amines were attempted under the optimized conditions to demonstrate the functionality of this method. The desired 4,5,6,7-tetrahydro-1*H*-indoles were obtained in good yield for 6l (68%) and high yields for **6m** and **6n** (88 and 94%). The structure of 4,5,6,7-tetrahydro-1*H*-indoles were confirmed with ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and X-ray crystallography (**6i**, CCDC 2164186). Gram scale reaction of **1a**, **2a**, and **3a** was also conducted (see SI), affording the product in 86% yield.

As noted above, when a bulkier group was present at the ortho position of arylamine (**6f** and **6i**, Table 3), the reaction slowed down and the yields decreased. A similar steric effect was also observed for benzoylmethylene malonates when the ortho positions on the phenyl ring were occupied (**4o**, Table 1). To investigate the mechanism of this reaction,[20,23] we decided to explore how steric effect affected the process of the reaction (Scheme 1). We selected **3i** where a moderately bulky

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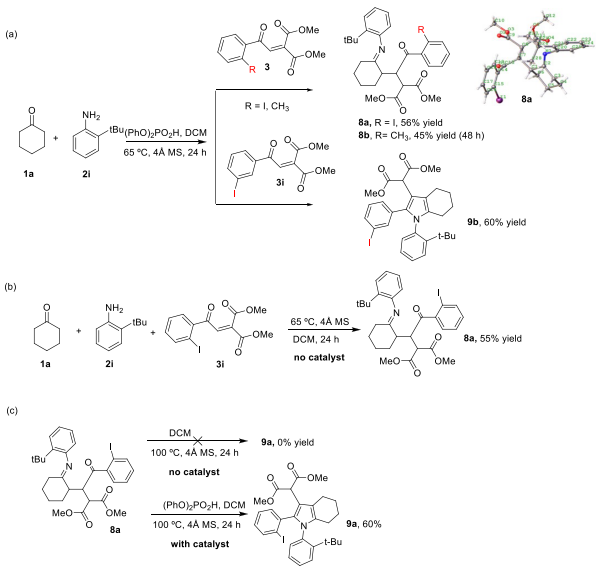
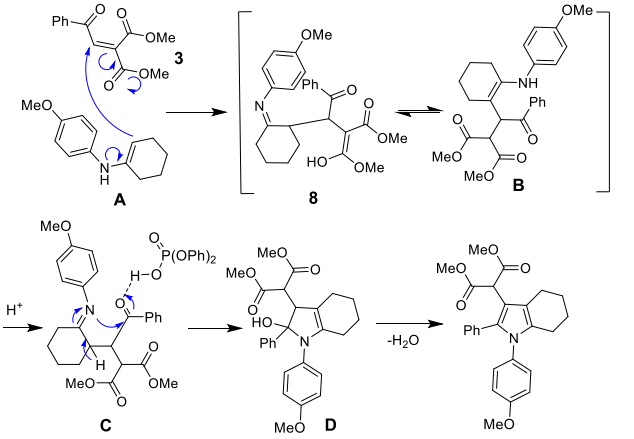
Scheme 1. Mechanism Investigation: (a) Steric Effect; (b, c) Catalyst Investigation



iodo group is present at the ortho position of the phenyl ring to react with *o*-*t*-butylaniline (**2i**) and cyclohexanone under optimized conditions (65 °C). As it turned out, no formation of 4,5,6,7-tetrahydro-1*H*-indole (**9a**) was detected (Scheme 1, a). Instead, another product was isolated as the major product (**8a**), which was identified as an imine intermediate confirmed via NMR spectroscopy, mass spectrometry, and X-ray crystallography (**8a**, CCDC: 2164187). Reaction of another benzoylmethylene malonate with a methyl group at the ortho position of the phenyl ring was also attempted, leading to similar results (**8b**). In sharp contrast, when the iodo group was placed at the meta position of the phenyl ring, the imine intermediate was not observed and 4,5,6,7-tetrahydro-1*H*-indole was isolated (**9b**). These data indicate that steric effects play an important role in this reaction. To prove that the imine is a synthetic intermediate in this reaction, **8a** in DCM was heated to 100 °C in the presence of $(PhO)_2PO_2H$, and 4,5,6,7-tetrahydro-1*H*-indole (**9a**) was obtained with 60% yield with unreacted **8a** still present in the reaction mixture, confirming that imine **8a** can be converted to **9a** (Scheme 1c).

To gain further insight into the mechanism, we investigated the role of the acid catalyst ($(PhO)_2PO_2H$). The reaction of **3i**, **1a**, and **2i** in the absence of an acid catalyst at 65 °C resulted in 55% yield of imine **8a** without observation of **9a**, similar to the result with the catalyst (**8a**, 56% yield) (Scheme 1b). When **8a** in DCM was heated to 100 °C without a catalyst, no product was observed, which is in sharp contrast with a similar reaction conducted in the presence of the acid catalyst (Scheme 1c). These data suggest that the acid catalyst, i.e., $(PhO)_2PO_2H$, plays a crucial role in the transformation of **8a** to **9a**. A mechanism of the reaction was proposed based on these experimental data (Scheme 2). Enamine **A** is formed *in situ* from cyclic ketone and arylamine, which then reacts with benzoylmethylene malonate (**3**) through a Michael-type addition to give **8**. An equilibrium between imine **8** and enamine **B** can be established. The carbonyl group is then activated by $(PhO)_2PO_2H$ to initiate an intramolecular cyclization reaction (**C**) to afford **D**, after which the loss of water provides the final 4,5,6,7-tetrahydro-1*H*-indole.

Scheme 2. Proposed Mechanism



3. CONCLUSIONS

In summary, we have developed a novel synthetic method to access 4,5,6,7-tetrahydro-1*H*-indoles/pentasubstituted pyrroles, which is of high biological and pharmaceutical importance. This three-component cascade reaction involving cyclic ketones, arylamines, and benzoylmethylene malonates is concise, versatile, and efficient, affording 4,5,6,7-tetrahydro-1*H*-indoles in high yields with wide substrate scopes. The three-component reaction is achieved through cooperative enamine-acid (Brønsted and metal Lewis acid) catalysis. Mechanistic studies indicate that the steric effect plays a crucial role in determining the output of the reaction. The formation of an imine intermediate was revealed and confirmed with X-ray crystallography. The Brønsted acid catalyst was proved to be the key to prompt the intramolecular cyclization reaction of the imine intermediate, leading to the form 4,5,6,7-tetrahydro-1*H*-indoles. Our DFT calculations suggest that 4,5,6,7-tetrahydro-1*H*-indoles with bulky groups could possess axial chirality (see SI). New reactions based on cooperative enamine-metal Lewis acid catalysis as well as the development of asymmetric catalytic methods to access 4,5,6,7-tetrahydro-1*H*-indoles with axial chirality are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05909.

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

Crystallographic data for the **6i** complex (CIF)

Crystallographic data for **8a** (CIF)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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