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Asymmetric Synthesis of α-Amino Ketones by Brønsted Acid Catalysis

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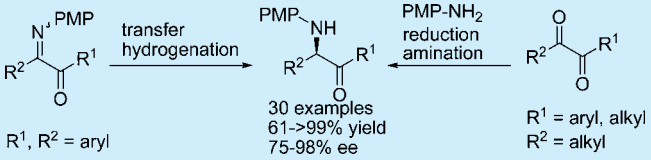
Supporting Information

ABSTRACT: The highly efficient, regioselective, and enantioselective transfer hydrogenation of α-keto ketimines and reductive amination of diketones by Brønsted acid catalysis is described. A series of chiral α-amino ketones is prepared in high yields (up to >99%), excellent regioselectivities (up to >99:1), and enantioselectivities (up to 98% ee). This method has broad substrate scope.



The development of new methods for the asymmetric synthesis of useful building blocks and the key structural units of biologically active compounds is one of the most important tasks currently facing organic chemists. α-Amino ketones are useful scaffolds in both synthetic and medicinal chemistry because they play a vital role in many biologically active natural products and pharmaceuticals[1] as well as being useful for the construction of structural diverse molecules.[2] Important examples of natural products containing a chiral α-amino ketone moiety include cathinone, which is a monoamine alkaloid isolated from Khat,[3a] and gelsemoxonine, which is an alkaloid found in *Gelsemium elegans*.[3b] Pharmaceutical compounds containing an α-amino ketone moiety include ketamine, which is used as an anesthetic,[3c] and Keto-ACE, which is an efficient agent for the treatment of hypertension[3d] (Figure 1). α-

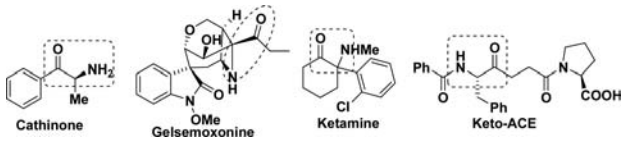


Figure 1. Representative biologically active compounds and pharmaceuticals containing α-amino ketone units.

Amino ketones can also be used as versatile building blocks for the synthesis of nitrogen- and oxygen-containing molecules, including 1,2-amino alcohols, which are used extensively in organic synthesis as chiral auxiliaries, ligands, and resolving reagents.[4] In light of their importance to synthetic and medicinal chemistry, the development of efficient new methods for the preparation of chiral α-amino ketones is of critical importance.[5]

Several excellent methods have been developed for the preparation of chiral α-amino ketones. In 2001, Maruoka and co-workers reported the development of the chiral quaternary ammonium salt-catalyzed Neber rearrangement of ketoximes for the construction of enantioenriched α-amino ketones.[6] Following on from this work, Miller and Ye developed new methods for the preparation of optically active α-amino ketones via the chiral carbene-catalyzed cross coupling of aldehydes with imines.[7] The research groups of Hashimoto,[8] Zhang,[9] Zhou,[10] Wulff,[11] and several other investigators[12] have also reported their work toward the synthesis of optically active α-amino ketones by asymmetric catalysis. Theoretically, the chiral α-amino ketones can be readily prepared via the catalytic asymmetric transfer hydrogenation of α-keto ketimines; however, there have been very few examples of this procedure in the literature. In fact, the only successful reported example of the utilization of this strategy was provided by Zhang's group in 2014, where they used chiral Lewis bases as catalysts to give the desired α-amino ketones in good yields and moderate to high enantioselectivities.[13] With this in mind, further work is required on this reaction to develop efficient and robust methods for the catalytic asymmetric transfer hydrogenation of α-keto ketimines. Given that chiral Brønsted acid catalysis[14] has been successfully used for the transfer hydrogenation of ketimines,[15] aldimines,[16] and α-ketimine esters,[17] we envisioned that Brønsted acids could be used as reasonable catalysts for the transfer hydrogenation of α-keto ketimines. Herein, we report the development of the first Brønsted acid catalyzed transfer hydrogenation of the prepared or in situ formed α-keto ketimines to give the corresponding α-amino ketones in high yields and excellent stereoselectivities. Notably, this reaction exhibited a broad substrate scope.

We first evaluated the transfer hydrogenation of α-keto ketimine **1a** with dihydropyridine **2a** in the presence of a catalytic amount of phosphoric acid **3a** (10 mol %). As expected, the target product α-amino ketone **4a** was obtained in 92% yield, albeit with a low enantioselectivity of 26% (Table 1, entry 1). In an attempt to improve the enantioselectivity of **4a**, we adjusted the substituents at the 3,3′-positions of the catalyst **3**. As shown in Table 1, the introduction of a bulky electron-donating substituent at the 3,3′-postitions of the catalyst gave catalyst **3b**, which gave a good yield for the reaction but a lower enantioselectivity of 20% (Table 1, entry 2). Catalysts **3c–f**

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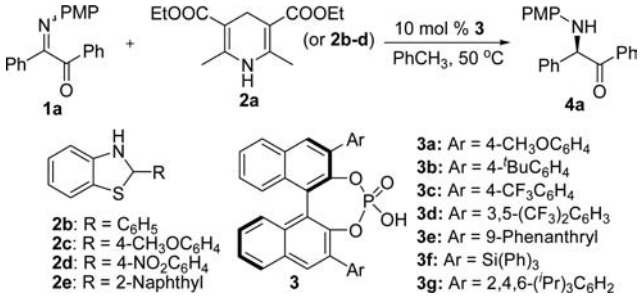
Table 1. Catalyst Screening and Optimization of the Reaction Conditions (PMP = *p*-Methoxyphenyl)[a]



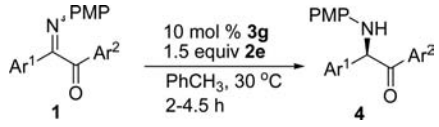
entry	3	2	time (h)	yield[b] (%)	ee[c] (%)
1	**3a**	**2a**	24	92	26
2	**3b**	**2a**	24	86	20
3	**3c**	**2a**	24	44	<5
4	**3d**	**2a**	24	51	<5
5	**3e**	**2a**	24	49	<5
6	**3f**	**2a**	24	trace	
7	**3g**	**2a**	24	46	95
8	**3g**	**2b**	3	71	89
9	**3g**	**2c**	3	86	89
10	**3g**	**2d**	3	51	78
11	**3g**	**2e**	3	90	93
12	**3g**	**2e**	3	94	93[d]
13	**3g**	**2e**	4	90	90[d,e]
14	**3g**	**2e**	4.5	92	95[d,f]

[a]Reaction conditions: α-keto ketimine **1a** (0.1 mmol), hydrogen donor **2a–e** (0.15 mmol), (*R*)-**3** (10 mol %), $PhCH_3$ (1 mL) at 50 °C; [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction conditions: α-keto ketimine **1a** (0.2 mmol), hydrogen donor **2e** (0.3 mmol), (*R*)-**3g** (10 mol %), $PhCH_3$ (1 mL) at 50 °C. [e]5 mol % of **3g** was used. [f]Reaction conducted at 30 °C.

also worked well for this reaction but gave the desired product **4a** in moderate yields with poor enantioselectivities (Table 1, entries 3–5). The phosphoric acid catalyst **3f** bearing a triphenylsilane group was found to be unsuitable as a catalyst for this reaction (Table 1, entry 6). Pleasingly, the 2,4,6-triisopropylphenyl-substituted phosphoric acid **3g** was found to be a good catalyst for this reaction in terms of the enantioselectivity of **4a** (95% ee), although the yield was moderate (Table 1, entry 7). A further period of optimization was then conducted in an attempt to improve the yield of this reaction. Dihydrobenzothiazoles have been reported to be efficient hydrogen donors in a wide range of transfer hydrogenation reactions.[18] With this in mind, we investigated the use of the 2-aryl-substituted dihydrobenzothiazoles **2b–e** as potential hydrogen sources for this transformation. The results of these experiments revealed that these alternative hydrogen sources significantly improved the rate of the reaction and gave the desired product **4a** with high yields and high enantioselectivities (Table 1, entries 8–11). The 2-naphthyl dihydrobenzo[*d*]thiazole (**2e**), in particular, was identified as the best hydrogen source for this reaction because it gave the desired product **4a** in 90% yield and 93% ee. The yield of **4a** could be further improved by increasing the concentration of the reaction (Table 1, entry 12). The catalyst loading and reaction temperature also affected the reaction results. For example, a reduction in the loading of the catalyst from 10 to 5 mol % led to a decrease in the yield and enantioselectivity of **4a** (Table 1, entry 13). The optimum results for the preparation of **4a** (92% yield, 95% ee) were obtained when the reaction was conducted at 30 °C (Table 1, entry 14).

With the optimal reaction conditions in hand, we proceeded to examine the substrate scope of this reaction using a series of α-keto ketimines bearing diaryl substituents (Table 2). First, the α-keto ketimines (**1b–k**) derived from symmetrical diaryl ketones were investigated. The results revealed that α-keto ketimines bearing para-substituted phenyl rings were excellent substrates for this transformation, regardless of the electronic properties of their substituents. For example, α-keto ketimine substrates bearing a para-substituted F, Cl, Br, or Me phenyl ring reacted smoothly to give the corresponding α-amino ketone products **4b–e** in excellent yields (89–95%) and enantioselectivities (95–96% ee) (Table 2, entries 2–5). α-Keto ketimine substrates bearing a meta-substituted phenyl ring (**4f–h**) were also converted to the corresponding α-amino ketones in excellent yields and enantioselectivities (Table 2, entries 6–8). The 3,4-2Cl phenyl- and 2-naphthyl-substituted α-keto ketimine substrates were readily hydrogenated under the optimal reaction conditions to give the corresponding α-amino ketones **4i,j** in excellent yields and enantioselectivities (Table 2, entries 9 and 10). Notably, the *N*-(4-chlorophenoxy)phenyl-substituted α-keto ketimine **1k** produced the target product **4k** in both excellent yield (92%) and enantioselectivity (94%) (Table 2, entry 11). As illustrated by Zhang's work,[13] the α-amino ketone **4k** can be used as a key intermediate for the synthesis of a cannabinoid receptor **1** (CBA) inhibitor. We found that the α-keto ketimine substrates bearing ortho-substituted phenyl rings did not perform well in this transformation, most likely because of steric hindrance from the ortho substituents on the phenyl rings. Second, we evaluated the suitability of a series of α-keto ketimines bearing different aryl substituents as substrates for the preparation of chiral α-amino ketones. Pleasingly, all of these substrates **1l–o** were converted to the corresponding products **4l–o** in high yields (61–92%) and excellent enantioselectivities

Table 2. Substrate Scope of Diaryl α-Keto Ketimines[a]



entry	1	4	Ar^1; Ar^2	yield[b] (%)	ee[c] (%)
1	**1a**	**4a**	Ph	92	95
2	**1b**	**4b**	4-FC_6H_4	91	95
3	**1c**	**4c**	4-ClC_6H_4	94	95
4	**1d**	**4d**	4-BrC_6H_4	89	96
5	**1e**	**4e**	4-MeC_6H_4	95	96
6	**1f**	**4f**	3-FC_6H_4	88	92
7	**1g**	**4g**	3-ClC_6H_4	97	93
8	**1h**	**4h**	3-MeC_6H_4	85	94
9	**1i**	**4i**	3,4-2ClC_6H_3	90	90
10	**1j**	**4j**	2-naphthyl	96	90
11	**1k**[d]	**4k**	C_6H_5	92	94
12	**1l**	**4l**	4-FC_6H_4; Ph	61	93
13	**1m**	**4m**	4-ClC_6H_4; Ph	81	91
14	**1n**	**4n**	4-BrC_6H_4; Ph	75	96
15	**1o**	**4o**	4-$MeOC_6H_4$; Ph	92	93

[a]Reaction conditions: α-keto ketimines **1** (0.2 mmol), hydrogen donor **2e** (0.3 mmol) and (R)-**3g** (10 mol %) in $PhCH_3$ (1 mL) at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC. [d]The 4-$CH_3OC_6H_4$ group of **1** was replaced by 4-(4-ClC_6H_4O)C_6H_4.

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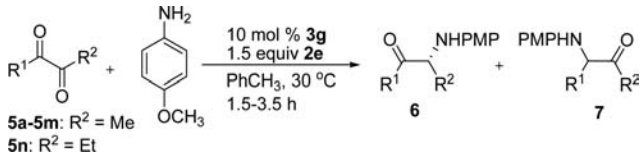
(91−94%). The absolute configuration of compound **4a** was assigned as *R* on the basis of a comparison of its optical rotation data with those reported in the literature.[11] The stereochemistries of products **4b−o** were assigned by analogy with that of **4a**.

We then proceeded to investigate the use of a series of 1,2-diketones bearing alkyl substituents (**5a−n**) as substrates in this reaction (Table 3). Our initial efforts were focused on the preparation of α-keto ketimines from alkyl-substituted 1,2-diketones. Unfortunately, however, the target imines were found to be unstable, which meant that they could not be efficiently isolated from the reaction mixture. Given that α-keto ketimines can be regioselectively prepared at the alkyl side of 1,2-diketones under mild reaction conditions,[19] we envisioned that it would be possible to achieve the catalytic asymmetric transfer hydrogenation of in situ generated α-keto ketimines. With this in mind, we evaluated the reaction of 1-phenylpropane-1, 2-dione **5a** with 4-methoxyaniline ($PMPNH_2$) and 2-naphthyldihydrobenzo[d]-thiazole **2e** under the optimal reaction conditions (200 mg of 5 Å MS was used as additive). As expected, the *N*-PMP-protected cathinone derivative **6a** was generated in high yield and excellent enantioselectivity (Table 3, entry 1). Based on this result, we went on to investigate several other diketones bearing alkyl groups in this reductive amination reaction. As shown in Table 3, aryl methyl diketones were excellent substrates for this transformation. For example, aryl methyl diketones bearing an electron-donating or electron-withdrawing substituent on their phenyl ring reacted smoothly to give the corresponding products in 67−93% yield and 95−98% ee (Table 3, entries 2−9). We noticed that the substrates bearing an electron-donating substituent of their phenyl ring gave better regioselectivities than those bearing an electron-withdrawing substituent (Table 3, entries 4, 5, and 8 vs 2, 3, 6 and 7). This difference in the regioselectivity was attributed to the electrophilicity of the carbonyl group adjacent to an electron-rich phenyl being lower than that of a carbonyl group adjacent to an electron-deficient phenyl, making it no more attractive to nucleophiles than the carbonyl on the alkyl side. Dialkyl diketones were also shown to be suitable substrates for this transformation. Under the optimal reaction conditions, we successfully prepared the α-amino ketones of substrates **5j−n** in high yields, good to excellent enantioselectivities, and high regioselectivities (Table 3, entries 10−14). To the best of our knowledge, this work represents the first reported example of the use of an alkyl-substituted 1,2-diketone in an organocatalyzed asymmetric reductive amination reaction. The absolute configuration of compound **6o** was assigned as *R* on the basis of a comparison of its optical rotation data with data reported in the literature.[12e] The stereochemistries of products **6a−n** were assigned by analogy with that of **6o**.

We carried out the asymmetric transfer hydrogenation of α-keto ketimine **1a** and the reduction amination of diketone **5a** on a gram scale (Scheme 1, eqs 1 and 2). The results of these reactions revealed that the catalyst loading and hydrogen donor equivalent could be decreased in these large-scale preparations. Notably, the highly optically active *N*-PMP-protected (*R*)-cathinone derivative **6a** could be produced on a gram scale in the presence of only 2 mol % of **3g** and 1.2 equiv of the hydrogen donor **2e** (Scheme 1, eq 2). Moreover, compound **6a** could be converted to the corresponding *N*-PMP-protected norephedrine compound **8a** in excellent yield, diastereoselectivity, and enantioselectivity (Scheme 1, eq 3).

In conclusion, we have developed a new method for the efficient asymmetric transfer hydrogenation of α-keto ketimines and the reductive amination of diketones for the synthesis of optically active α-amino ketones. This reaction was found to be amenable to both symmetrical and unsymmetrical diaryl α-keto ketimines, including aryl alkyl- and dialkyl-substituted diketones, with the corresponding α-amino ketones being produced in excellent yields and high stereoselectivities. These α-amino ketone products are useful intermediates for the preparation of optically active amino alcohols, and some of them could be used to synthesize chiral natural alkaloid derivatives.

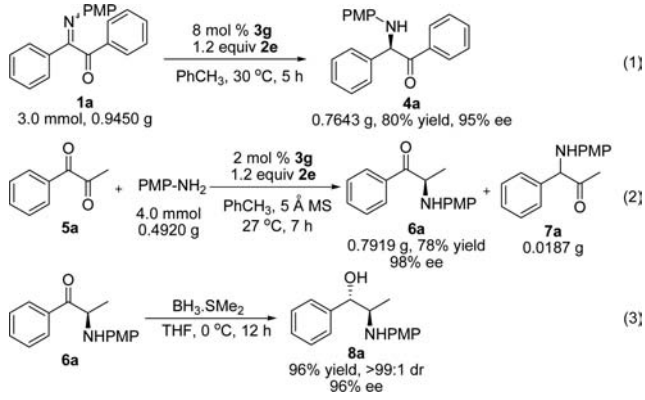
Table 3. Substrate Scope of Alkyl-Substituted Diketones[a]



entry	5	6	R^1	yield[b] (%)	6:7[c]	ee[d] (%)
1	**5a**	**6a**	C_6H_5	85	>99:1	98
2	**5b**	**6b**	4-ClC_6H_4	67	97:3	98
3	**5c**	**6c**	4-$CF_3C_6H_4$	91	91:9	95
4	**5d**	**6d**	4-MeC_6H_4	91	>99:1	98
5	**5e**	**6e**	4-$MeOC_6H_4$	93	>99:1	97
6	**5f**	**6f**	3-FC_6H_4	74	98:2	96
7	**5g**	**6g**	3-$CF_3C_6H_4$	72	98:2	98
8	**5h**	**6h**	3-MeC_6H_4	80	>99:1	98
9	**5i**	**6i**	2-Naphthyl	71	99:1	96
10	**5j**	**6j**	Me	84		75
11	**5k**	**6k**	Et	75	89:11	95
12	**5l**	**6l**	^{n}Pr	69	93:7	97
13	**5m**	**6m**	^{n}Bu	77	93:7	95
14	**5n**	**6n**	Et	89		92
15	**5a**	**6o**[e]	C_6H_5	>99		79

[a]Reaction conditions: 1, 2-diketones **5** (0.3 mmol), $PMPNH_2$ (0.2 mmol), hydrogen donor **2e** (0.3 mmol), (*R*)-**3g** (10 mol %), and 5 Å MS (200 mg) in $PhCH_3$ (1 mL) at 30 °C. [b]Isolated yield. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC. [e]The aniline was used instead of *p*-methoxyaniline.

Scheme 1. Gram-Scale Synthesis of α-Amino Ketones 4a and 6a and the Asymmetric Synthesis of Amino Alcohol 8a from 6a



■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization, and ^{1}H NMR, ^{13}C NMR, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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