Communication

Copper(I)-Catalyzed Enantioselective Incorporation of Ketones to Cyclic Hemiaminals for the Synthesis of Versatile Alkaloid Precursors

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Copper(I)-Catalyzed Enantioselective Incorporation of Ketones to Cyclic Hemiaminals for the Synthesis of Versatile Alkaloid Precursors

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Supporting Information

ABSTRACT: A general catalytic enantioselective method that can produce 5, 6, and 7-membered *N*-heterocycles possessing various ketone moieties was developed, starting from stable and easily available cyclic hemiaminals and ketones. The method involves three successive steps in one pot (aldol addition, dehydration, and enantioselective intramolecular aza-Michael reaction), all of which are promoted by a chiral copper(I)–conjugated Brønsted base catalyst. This method is useful for a rapid access to versatile chiral building blocks for the synthesis of drug lead alkaloids.

Chiral nitrogen-containing heterocycles (*N*-heterocycles) are ubiquitous structural motifs in natural products, synthetic pharmaceuticals, and chiral catalysts. Specifically, functionalized pyrrolidines and piperidines are fundamental components of naturally occurring pyrrolidine and piperidine alkaloids,[1] which are further assembled to construct more complex structures, such as indolizidine and quinolizidine alkaloids.[2] In nature, chiral pyrrolidine and piperidine alkaloids are synthesized through enzyme-catalyzed Mannich-type reactions between enolates derived from acetyl-CoA or acetoacetyl-CoA and cyclic imine/iminium intermediates **1**, as a key enantioselective carbon–carbon bond-forming step (Figure 1a).[3] Subsequent structural modifications of **2**—e.g., decarboxylation and ring-formation—afford various alkaloid structures. Thus, **2** is a general chiral intermediate for the synthesis of various alkaloids.

Chirality control in the Mannich-type reaction of simple cyclic imine/iminium intermediates **1** by artificial asymmetric catalysts, however, is notoriously difficult. Onomura *et al.* reported the first example of a catalytic enantioselective enolate addition to an *N*-acyl pyrrolidine-derived iminium cation using a Lewis acid catalyst,[4] but the enantioselectivity was not satisfactory (up to 53% ee). More recently, Bella and coworkers reported a proline-catalyzed Mannich reaction of piperidine-derived imines.[5] Although the enantioselectivity is high, the high catalyst loading (20–100 mol %), long reaction time (7–30 days), and moderate product yields may hamper its application to alkaloid syntheses. Thus, despite the high versatility of **2**, a synthetically useful catalytic enantioselective method to access them has yet to be developed. The lack of a useful method is partly due to the chemical lability of intermediate **1**.[6] Previously reported catalytic asymmetric Mannich-type reactions of cyclic imine/iminium substrates with significant efficiency are limited to the use of stabilized substrates derived from isoquinolines,[7] carbolines,[8] and indoles.[9] Still, these methods cannot produce *N*-heterocycles with differing ring sizes. To realize more general catalytic asymmetric synthesis of **2**, an alternative pathway without the intermediary of unstable **1** is necessary. Here we report the first such method by devising the reaction pathway (Figure 1b).

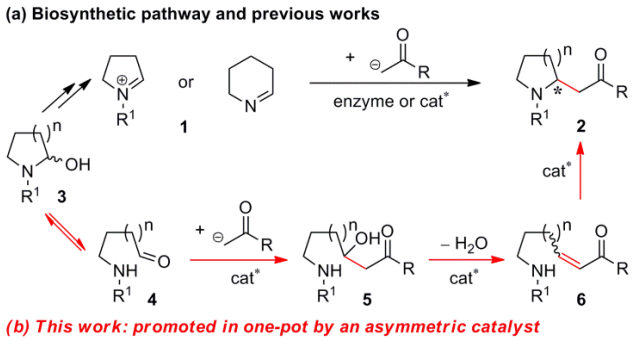
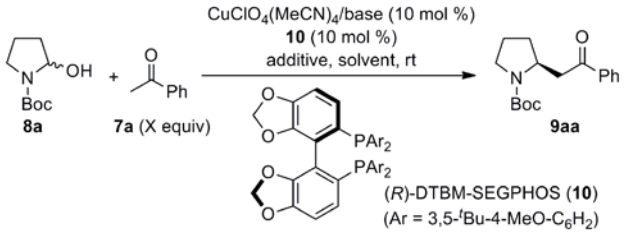


Figure 1. Two catalytic enantioselective pathways for the synthesis of versatile intermediate **2** in alkaloid synthesis.

To overcome the obstacles in the catalytic enantioselective synthesis of **2**, we designed a one-pot, three-step pathway starting from stable and easily available cyclic hemiaminal **3**, existing under equilibrium with linear aldehyde **4** (Figure 1b). This pathway involves; (1) chemoselective deprotonation of ketones and subsequent aldol addition of the thus-generated enolate[10] to **4**, affording **5**, (2) dehydration of **5** to produce enone **6**, and (3) intramolecular enantioselective aza-Michael reaction[11] to produce **2**. Copper(I) alkoxide–chiral phosphine complexes are a unique chiral Brønsted base catalyst, which

could efficiently promote all the three reaction steps.[12] Due to the mismatched nature of a copper(I) (soft metal)–alkoxide (hard anion) conjugate, the catalyst demonstrates high Brønsted basicity. In addition, copper(I)–phosphine complexes are generally stable to polar functional groups and protic compounds, including water generated in this designed pathway. Thus, we began by examining various copper alkoxide–chiral phosphine complexes in the asymmetric introduction of ketone **7a** to 5-membered hemiaminal **8a** (Table 1).

Table 1. Optimization Study of the Catalytic Enantioselective Introduction of 7a to 8a.



entry	X	solvent	base	time (h)	yield (%) [a]	ee (%) [b]
1	3	THF	LiO^{t}Bu	7	88	82
2[c]	3	THF	LiO^{t}Bu	13	40	91
3	3	TBME	LiO^{t}Bu	13	97	88
4[d]	3	TBME	LiO^{t}Bu	13	93	92
5[d]	2.5	TBME	KO^{t}Bu	13	99	94
6[d]	1.5	TBME	KO^{t}Bu	24	99	95
7[d,e]	1.5	TBME	KO^{t}Bu	72	60	94

[a] Determined by ^{1}H NMR using an internal standard. [b] Determined by HPLC using a Chiralpak AY-H column. [c] 4Å Molecular sieves (4Å MS: 250 g/mol) was added. [d] 10 mol % H_2O was added. [e] Catalyst loading = 2.5 mol %.

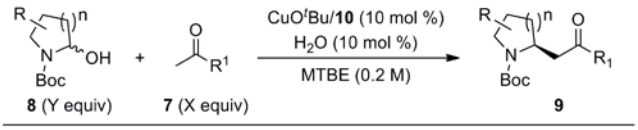
The ring-opened aldehyde form **4** (R^1 = Boc, n = 1) was not detectable in a solution of **8a** by NMR under neutral conditions. Still, the desired reaction proceeded, and product **9aa** was obtained in variable yields, depending on the chiral phosphine ligands used.[13] Preliminary investigation revealed that (*R*)-DTBM-SEGPHOS (**10**) produced the highest reactivity and enantioselectivity among the ligands investigated. The reaction proceeded smoothly using 10 mol % of CuO^{t}Bu (generated *in situ* from $CuClO_4$•$4CH_3CN$ and LiO^{t}Bu)[14]/**10** in THF at room temperature, affording product **9aa** in 88% yield and 82% ee (entry 1). The use of other copper(I) sources, such as $CuBF_4$ and CuOTf, produced comparable results. On the other hand, product **9aa** was obtained in only 35% yield in the absence of a copper source (i.e., LiO^{t}Bu-catalyzed reaction). The addition of 4Å MS as a desiccant improved the enantioselectivity to 91%, but the yield was markedly decreased (entry 2). A survey of solvents led us to identify *tert*-butyl methyl ether (TBME) as the best solvent, giving **9aa** in 97% yield with 88% ee (entry 3). Importantly, the addition of 10 mol % H_2O to the reaction mixture improved the enantioselectivity to 92%, without a significant loss of catalyst activity (entry 4). The use of KO^{t}Bu instead of LiO^{t}Bu as a base further improved the enantioselectivity to 94% (entry 5). Finally, product **9aa** was obtained in 99% yield with 95% ee in the presence of 1.5 equiv of acetophenone (**7a**) in TBME for 24 h at room temperature (entry 6). Catalyst loading could be reduced to 2.5 mol %, giving **9aa** in 60% yield with 94% ee by extending the reaction time to 72 h (entry 7). Notably, a self-aldol reaction of hemiaminal **8a** was not observed in any of the entries. Chemoselective enolate formation from ketone **7a** in the presence of the aldehyde form derived from hemiaminal **8a** likely occurred due to their large concentration difference in the reaction mixture.

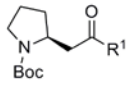
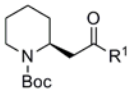
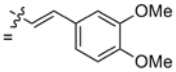
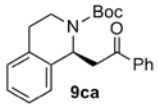
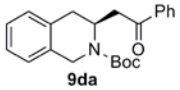
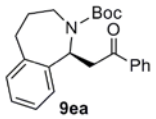
Although satisfactory results were obtained from 5-membered hemiaminal **8a**, the conditions optimized for **8a** were not directly applicable to 6-membered hemiaminals. For example, the reaction between tetrahydroisoquinoline-derived hemiaminal **8c** and **7a** afforded product **9ca** in only 20% yield, albeit with 97% ee (50 °C for 45 h). The use of mesitylcopper,[15] instead of CuO^{t}Bu, in the absence of added water slightly improved the yield without markedly changing the enantioselectivity. The moderate yield in the case of **8c** was likely due to a lower concentration of the reactive aldehyde form than in the case of **8a**. To increase the concentration of the aldehyde form, we studied effects of additive achiral bases.[13] As expected, **9ca** was produced in quantitative yield with 94% ee in the presence of 0.5 equiv Cs_2CO_3.

The substrate scope of this reaction was then studied under the optimized conditions, and the results are summarized in Table 2. By fixing hemiaminal to **8a**, nucleophile ketones were first surveyed (entries 1–17). Products were obtained in high yield and enantioselectivity for aryl ketones containing both electron-donating and electron-withdrawing substituents at the *ortho*-, *meta*- and *para*-positions. Ester and nitro functionalities were well tolerated (entries 5–6). Aryl ketone **7h** containing an electron-donating *p*-methoxy group was less reactive than other aryl ketones. Therefore, the reaction was performed at 50 °C for 24 h, and product **9ah** was obtained in 67% yield with 90% ee (entry 9). Heteroaryl ketones **7j** and **7k,** possessing coordinating heteroatoms with the catalyst, were also competent, and products were obtained in excellent yield and enantioselectivity (entries 11–12). Furthermore, enones and ynones also served as excellent nucleophiles (entries 13–15). Potential byproducts through 1,4-addition of ketones were not detected at all in these entries. Importantly, this reaction was applicable to aliphatic ketones **7o** and **7p** with only a slight decrease in enantioselectivity compared to aromatic ketones (entry 16-17).

The scope of the hemiaminal side was examined next (Table 2, entries 18–22). In addition to the 5-membered pyrrolidine-derivatives, this reaction can be extended to the synthesis of 6-membered piperidine- and tetrahydroisoquinoline-derivatives (entries 18–21). Specifically, **9da** containing a substituent at the C-3 position of the tetrahydroisoquinoline core is difficult to synthesize by other methods. Most of the reactions affording 6-membered heterocycles were conducted in the presence of a Cs_2CO_3 additive. In the case of 7-membered hemiaminal **8e**, the ring-opened aldehyde form

Table 2. Substrate Scope.[a]



entry	product	X/Y	temp. (°C)	time (h)	yield[b] (%)	ee[c] (%)
						
1[d]	**9aa**: R^1 = Ph	1.5/1	25	24	98	95
2	**9ab**: R^1 = *p*-Br-C_6H_4	1.5/1	25	24	90	95
3	**9ac**: R^1 = *m*-Br-C_6H_4	1.5/1	25	24	82	91
4	**9ad**: R^1 = *o*-F-C_6H_4	1.5/1	0	48	65	94
5[e]	**9ae**: R^1 = *p*-$CH_3OC(O)C_6H_4$	1/1.5	0	24	80	97
6	**9af**: R^1 = *p*-NO_2-C_6H_4	1/1.5	0	24	98	96
7[f]	**9af**: R^1 = *p*-NO_2-C_6H_4	1/1.5	25	36	93	94
8[d]	**9ag**: R^1 = *p*-CH_3-C_6H_4	1.5/1	25	24	85	92
9	**9ah**: R^1 = *p*-CH_3O-C_6H_4	1.5/1	50	24	67	90
10	**9ai**: R^1 = 2-naphthyl	1.5/1	25	24	89	93
11	**9aj**: R^1 = 2-thiophene	1.5/1	25	24	96	92
12	**9ak**: R^1 = 3-pyridine	1/1.5	0	24	95	97
13	**9al**: R^1 = (*E*)-CH=CHPh	1.5/1	25	24	99	96
14	**9am**: R^1 = (*E*)-CH=CHC_3H_7	1.5/1	25	24	73	97
15[g]	**9an**: R^1 = CCC_2H_5	1.5/1	50	48	55	97
16[h]	**9ao**: R^1 = $(CH_2)_2$Ph	1.5/1	50	24	81	84
17[h]	**9ap**: R^1 = CH_2CH_3	3/1	50	24	68	89
						
18[d,e]	**9ba**: R^1 = Ph	1/1.5	25	24	99	98
19	**9bb**: R^1 = 	1/1.5	25	48	75	97
20[e,h]	 **9ca**	1/3	50	48	99	94
21[e,h]	 **9da**	1/1.5	50	48	95	94
22[i]	 **9ea**	1/3	50	48	52	96

[a] The reaction was performed in 0.2-mmol scale under the general conditions in the scheme unless otherwise noted. CuO^{t}Bu was generated from $CuClO_4$•$4CH_3CN$ + KO^{t}Bu. [b] Isolated yields. [c] Determined by HPLC using a chiral column. [d] Absolute configuration was determined to be (*S*). [e] 0.5 equiv of Cs_2CO_3 was added. [f] 0.4-mmol scale reaction using 2.5 mol % of catalyst. [g] 2.0-mmol scale reaction using 5 mol % of catalyst. [h] Using mesitylcopper instead of CuO^{t}Bu without adding H_2O. [i] Using 20 mol % of mesitylcopper/**10** as a catalyst.).

was the predominant species based on NMR analysis. Despite the existence of the aldehyde form in a significant concentration, product **9ea** was obtained in only 33% yield albeit with 99% ee in the presence of 10 mol % catalyst (50 °C for 24 h). An (*E*)-enone intermediate (corresponding to **6** in Figure 1) was obtained as the main side product (67%). Therefore, the aza-Michael reaction step was the rate-determining step of the overall process in the case of the 7-membered hemiaminal substrate. Fortunately, the yield of **9ea** improved to 52% in the presence of 20 mol % catalyst with maintaining the excellent enantioselectivity (96% ee, entry 22). Therefore, the current method is noteworthy for its high adaptability to multiple distinct requirements depending on the substrate in one-pot, multi-event processes.

Enantiomerically-enriched functionalized *N*-heterocycles obtained by the catalytic method developed in this study have broad synthetic utility.[13] Removal or reduction of the Boc group of **9aa** or **9ba** and diastereoselective reduction of the ketone carbonyl group will lead to various sedum alkaloids.[16] Cleavage of the Boc group of **9bb** and subsequent treatment of the product with a base selectively afforded *trans*- and *cis*-quinolizidinones **11** and **12**, depending on the conditions of the base treatment (Figure 2).[17] Both **11** and **12** are key intermediates for the synthesis of quinolizidine alkaloids, such as (+)-lasubine I,[18a] (–)-lasubine II,[18b] and (–)-decinine.[18c] The same two-step procedure from pyrrolidine derivative **9am** produced a *cis*-indolizidinone in 90% yield with an excellent diastereomer ratio (d.r. > 20:1), which is a key intermediate for the synthesis of indolizidine (–)-167B.[13,18d]

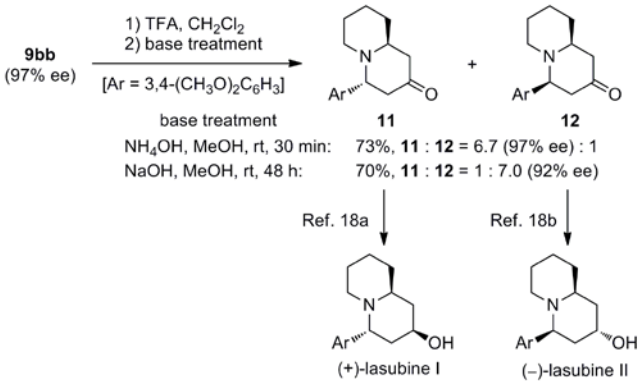


Figure 2. Representative valuable conversions of the products.

We believe that this reaction proceeds through the three step sequence as designed in Figure 1b based on the following results (Figure 3). First, product **9aa** was not obtained at all when protected aminal **13** was used as a substrate instead of hemiaminal **8a** under the optimized conditions (eq. 1). This finding suggests that the reaction does not proceed via the cyclic iminium cation **1**, which might be generated from **8** through dehydration. Second, subjecting isolated enone **6aa** to the reaction conditions afforded **9aa** in quantitative yield with 93% ee (eq. 2). The enantioselectivity was comparable to the reaction starting from **7a** and **8a** (Table 2, entry 1), supporting the notion that **6** is the catalytic cycle intermediate. Third, aldol intermediate **5aa** was synthesized and subjected to the present reaction conditions (eq. 3). The starting **5aa** quickly disappeared, generating ketone **7a** and hemiaminal **8a** as detected by TLC analysis. After 12 h, **9aa**

was obtained in 48% yield with 91% ee. Thus, aldol **5** is not stable under the reaction conditions, but is an intermediate of the catalytic cycle. Together, these findings support the three-step, one-pot pathway proposed in Figure 1b.[19]

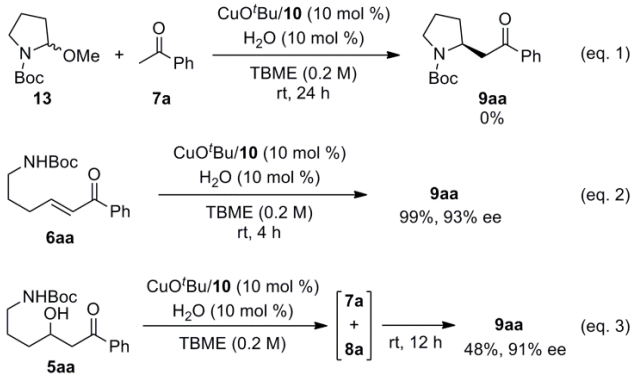


Figure 3. Mechanistic supports.

In conclusion, we developed a catalytic enantioselective method for the introduction of ketones to hemiaminals. This is the first catalytic enantioselective method for introducing various ketones to *N*-heterocycles with differing ring sizes (5-, 6-, and 7-membered ring). The process comprises three distinct steps in one pot, all of which are promoted by the chiral copper(I)-conjugated Brønsted base catalyst. This method offers general and straightforward access to enantiomerically-enriched versatile precursors for alkaloid and drug syntheses, including pyrrolidines, piperidines, indolizidines, quinolizidines, tetrahydroisoquinolines, and tetrahydrobenzazepines, starting from stable and easily available substrates.

Supporting Information

Experimental details including procedures, synthesis and characterization of all new products, and supporting data for mechanistic insights. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) This finding indicates that **11** was the kinetic product, and epimerization proceeded selectively at the benzylic position through an iterative retro-aza-Michael reaction and aza-Michael reaction, affording thermodynamically more favorable **12**.
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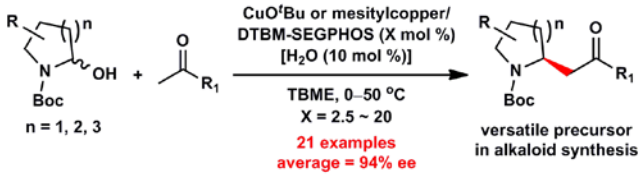
(19) For a proposed catalytic cycle, please see SI.


R
n
OH
N
Boc
n = 1, 2, 3
O
R1
CuO^{t}Bu or mesitylcopper/
DTBM-SEGPHOS (X mol %)
[H2O (10 mol %)]
TBME, 0–50 °C
X = 2.5 ~ 20
21 examples
average = 94% ee
versatile precursor
in alkaloid synthesis