Asymmetric Catalysis

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Catalytic Asymmetric Tandem Reaction of Tertiary Enamides: Expeditious Synthesis of Pyrrolo[2,1-*a*]isoquinoline Alkaloid Derivatives

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Abstract: *Reported is a new and efficient strategy for rapid construction of the chiral tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one structure from unique tertiary enamide synthons. A $Cu(OTf)_2$/chiral Pybox complex catalyzes the intramolecular enantioselective addition of tertiary enamides to ketonic carbonyls with subsequent diastereoselective interception of the resulting acyliminium by tethered electron-rich aryl moiety. The tandem reaction produces diverse tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one derivatives as the sole diastereoisomers in good to excellent yields with up to 98.5 % ee. The transformations of the resulting heterocycles into various hexahydropyrrolo[2,1-a]isoquinoline derivatives were also demonstrated. The cyclization products, which are difficult to obtain by other synthetic means, are structural motifs found in many bioactive alkaloids.*

Hexahydropyrrolo[2,1-*a*]isoquinoline and tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one structures occur widely in natural products. Depicted in Figure 1 are some representative examples including (+)-crispine,[1] (−)-trolline,[2] (+)-oleracein,[3] annosequaline,[4] and erythrina alkaloids[5] such as erysotramidine[6] and erythrosotidienone.[7] Most of the pyrrolo[2,1-*a*]isoquinoline alkaloids display remarkable antitumor, antibacterial, antiviral, and antioxidizing activities[8] while erythrina alkaloids are well-known for their curare-like activity in addition to hypertensive, sedative, and CNS depressant properties.[5] Because of unique fused heterocyclic ring structures and diverse pharmacological activities, these alkaloids are very popular and attractive targets for synthetic organic chemists. Despite the many elegant synthetic methods documented in the literature,[5,8] catalytic enantioselective synthesis of (+)-crispine, (−)-trolline, (+)-oleracein, and their analogues is rare. The groups of Czarnoki[9] and Zhou[10] achieved the synthesis of (+)-crispine through a ruthenium-catalyzed asymmetric transfer hydrogenation and an iridium-catalyzed asymmetric hydrogenation of the carbon–carbon double bond of 8,9-dimethoxy-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline, respectively. The methods, however, require the preparation of a fused heterocyclic ring precursor. In a multistep synthesis of (+)-crispine reported by Itoh and co-workers,[11] the CuCl/(*S*)-Tol-BINAP-catalyzed allylation of 3,4-dihydroisoquinoline with allyltrimethoxysilane is involved as a key step which produces (*R*)-1-allyl-1,2,3,4-tetrahydroisoquinoline in 91 % yield and 71 % *ee*. To the best of our knowledge, the de novo construction of hexahydropyrrolo[2,1-*a*]isoquinoline and tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one structures in catalytic enantioselective manner is not known.

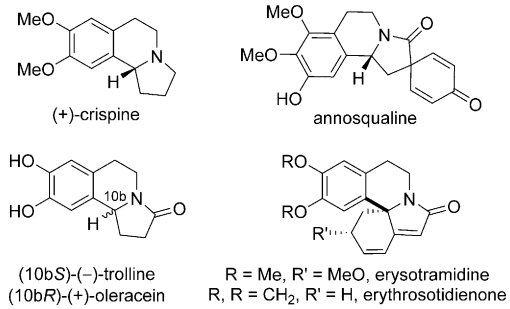

Figure 1. Structures of some pyrrolo[2,1-*a*]isoquinoline alkaloids.

Being enamine variants, tertiary enamides exhibit diminished nucleophilicity because of the presence of an electron-withdrawing acyl group on the nitrogen atom.[12] Therefore they have long been known as stable and marginally useful chemical entities in synthesis.[13,14] The notion has been challenged, however, in recent years. Structural analysis reveals a cross-conjugation system within tertiary enamides. The enabled regulation of the cross-conjugation system by means of either electronic and steric effects of the substituents on the enamide segment, or by varying the polarity of the reaction media could enhance the delocalization of the lone-pair electrons of the nitrogen atom into the carbon–carbon double bond to revive the nucleophilicity of tertiary enamides. In the past years we have endeavored to explore the nucleophilic reactions and synthetic applications of stable tertiary enamides, thus demonstrating tertiary enamides are unique and shelf-stable, yet versatile synthons in synthesis.[14]

Our previous work has evidenced that enaminic reactions of tertiary enamides with electrophiles such as carbonyl,[15] imine,[16] nitrilium,[17] and epoxides[18] form acyliminium intermediates which undergo deprotonation to afford N-heterocyclic products (Figure 2). We envisioned that intra-

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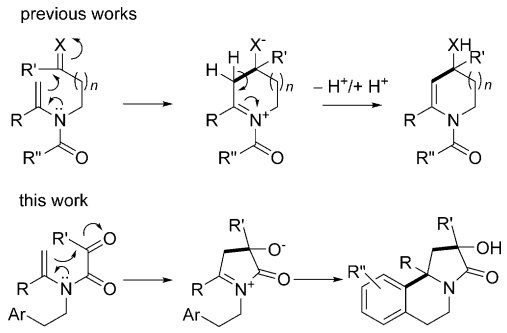
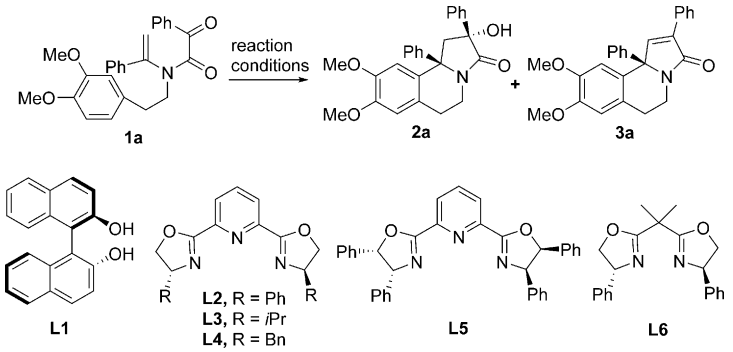


Figure 2. Strategies for the synthesis of N-heterocyclic compounds based on tertiary enamides.

molecular interception of an acyliminium by a nucleophile would generate a fused heterocyclic ring. We disclose herein a catalytic enantioselective reaction cascade involving nucleophilic addition of tertiary enamides to ketonic carbonyls and the trapping of acyliminium by a benzene moiety. The method is highly efficient and enantio- and diastereoselective, thus leading to diverse tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one derivatives with enantiomeric excess of up to 98.5% (Figure 2).

We commenced our study with the examination of the reaction of the tertiary enamide **1a** (for structure see Table 1). As a prelude to asymmetric catalysis, Lewis acids were tested and $Sn(OTf)_2$ was found efficient to catalyze the designed tandem reaction to yield the racemic product **2a** in 90% yield. In addition to **2a**, the dehydration compound **3a** was also isolated in 10% yield (see Tables S1 and S2 in the Supporting Information). The outcomes encouraged us to screen a number of chiral Lewis acids to achieve catalytic enantioselective construction of the tetrahydropyrrolo[2,1-*a*]isoquinolin-3-(2*H*)-one structure. We firstly looked at the performance of a few chiral salen/metal complexes, which were validated in catalyzing the enantioselective addition of tertiary enamides to ketones.[15a] Surprisingly they either did not show any catalytic activity at all or gave the monocyclic product rather than the desired bicyclic compounds, **2a** or **3a** (Table S3). It was also disappointing that both chiral aluminum monophosphates and chiral thioureas gave no enantiocontrol or very low activity (see Table S4). The complexes of chiral binol derivatives with $Ti(OiPr)_4$ were then scrutinized. As summarized in Table 1, the titanium (*R*)-binolate-catalyzed reaction proceeded smoothly at ambient temperature to form **3a** almost quantitatively. The use of Na_2CO_3 to inhibit possible acid-assisted dehydration did not change the reaction pathway, with **3a** being isolated in 93% yield. Frustratingly, no asymmetric induction was observed (entries 1 and 2). The combination of $Ti(OiPr)_4$ with other chiral binol derivatives did not improve the reaction. For example, while a 5,5′,6,6′,7,7′,8,8′-octahydrobinol/$Ti(OiPr)_4$ complex gave virtually no enantioselectivity, the titanium catalysts derived from 3,3′-disubstituted chiral binols appeared completely inert (see Table S5). When we turned our attention to chiral Pybox ligands,[19] we discovered that the copper complex of the ligand **L2** catalyzed the tandem reaction of **1a** with excellent enantio- and diastereoselectivity. A single diastereoisomer, (2*R*,10b*R*)-2-hydroxy-8,9-dimethoxy-2,10b-diphenyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3-(2*H*)-one (**2a**) with 99.2% *ee* was obtained as the sole product in 51% yield (entry 3). The zinc and tin complexes with **L2** led to diminished catalytic efficiency and selectivity (entries 4 and 5). Interestingly, the ligand **L5** acted just as well as **L2**, while the other Pybox ligands **L3** and **L4**, and bisoxazoline **L6**[20] displayed low activity and poor enantioselectivity, thus indicating the beneficial effect of the phenyl substituent on the oxazoline moiety of Pybox ligands (entries 6–9). To improve the productivity, other reaction parameters were further optimized. It is important to note that dichloromethane (DCM) is an ideal solvent as all other solvents, including tetrahydrofuran, acetonitrile, chloroform, benzene, toluene, xylene, and *N*,*N*-dimethylformamide, have a detrimental effect on asymmetric catalysis (see Table S6). The employment of additives ranging from TsOH to DIPEA and Na_2CO_3 retarded the reaction (see Table S6). In contrast, introduction of hexafluoroisopropanol (HFIP) facilitated the

Table 1: Development of catalytic enantioselective tandem reaction.



Entry	Cat. (0.1 equiv)	Additive (equiv)	Solvent	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%]
1	**L1**/$Ti(OiPr)_4$	–	DCM	RT	6	**3a** (97)	0
2	**L1**/$Ti(OiPr)_4$	Na_2CO_3 (0.2)	DCM	RT	6	**3a** (93)	0
3	**L2**/$Cu(OTf)_2$	–	DCM	RT	15	**2a** (51)	99.2
4	**L2**/$Zn(OTf)_2$	–	DCM	RT	15	**2a** (30)	93.5
5	**L2**/$Sn(OTf)_2$	–	DCM	RT	15	**2a** (41)	78.3
6	**L3**/$Cu(OTf)_2$	–	DCM	RT	15	**2a** (60)	72.8
7	**L4**/$Cu(OTf)_2$	–	DCM	RT	15	**2a** (< 20)	n.d.[c]
8	**L5**/$Cu(OTf)_2$	–	DCM	RT	15	**2a** (58)	94.8
9	**L6**/$Cu(OTf)_2$	–	DCM	RT	15	**2a** (37)	21.5
10	**L2**/$Cu(OTf)_2$	HFIP (1)	DCM	RT	2	**2a** (64)	95.6
11	**L2**/$Cu(OTf)_2$	HFIP (2)	DCM	RT	2	**2a** (76)	98.3
12	**L2**/$Cu(OTf)_2$	HFIP (3)	DCM	RT	2	**2a** (68)	98.6
13	**L2**/$Cu(OTf)_2$	HFIP (2)	DCM	30	0.5	**2a** (84.5)	95.6
14	**L2**/$Cu(OTf)_2$	HFIP (2)	DCM	reflux	0.5	**2a** (75)	n.d.[c]
15	**L2**/$Cu(OTf)_2$	HFIP (2)	DCM	0	2	**2a** (72)	93.0
16	**L2**/$Cu(OTf)_2$	HFIP (2)	DCM	−40	24	**2a** (0)	–
17	**L5**/$Cu(OTf)_2$	HFIP (2)	DCM	30	0.5	**2a** (42)	92.0
18	**L5**/$Cu(OTf)_2$	–	DCM	30	1	**2a** (83)	93.1

[a] Yield of isolated product. [b] Measured by chiral-phase HPLC. [c] Not determined. Tf = trifluoromethanesulfonyl.

transformation of **1a** (entries 10–12). After final examination of the temperature effect, it appeared that the highest chemical yield along with excellent enantioselectivity was obtained when the bicyclization of **1a** was performed in DCM at 30 °C in the presence of HFIP (2 equiv) and a catalytic amount of $Cu(OTf)_2$/**L2** (entries 13–16). It is noteworthy that the complex between $Cu(OTf)_2$ and **L5**, an alternative to the $Cu(OTf)_2$/**L2** catalyst, exhibited remarkable catalytic activity and enantioselectivity. It catalyzed the efficient formation of highly enantiopure **2a** in 83% yield at 30 °C, even in the absence of HFIP (entries 17 and 18).

Under the optimized reaction conditions using either $Cu(OTf)_2$/**L2** (entry 13, Table 1) or $Cu(OTf)_2$/**L5** (entry 18, Table 1), the scope of the catalytic asymmetric synthesis of tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one derivatives was investigated. As illustrated in Figure 3, although the $Cu(OTf)_2$/**L2**-catalyzed reaction of **1a** afforded **2a** in 84% yield with 95.6% *ee*, the same reaction of the substrates **1b–c** gave the corresponding products **2b–c** in markedly decreased yields and enantioselectivity. To our delight, the complex of $Cu(OTf)_2$ with the chiral **L5** acted as a more efficient catalyst to transform all tertiary enamides into highly enantioenriched fused N-heterocyclic products. First of all, the reaction of tertiary enamides (**1a–e**), which contain a substituted aryl group at the α position, produced the compounds **2a–e** in 74–83% yield and 88.3–98.3% *ee* irrespective of the electronic nature of a substituent and its substitution pattern on the benzene ring. The alkyl-substituted tertiary enamide **1f** underwent the same reaction to give **2f**, albeit in slightly lower yield and *ee*. Secondly, in addition to 1,2-dimethoxyphenyl, electron-rich aromatic components such as 1,3-dimethoxyphenyl and piperonyl in the reactants **1** were also capable of intercepting the acylininium intermediate, thus enabling the preparation of the tricyclic compounds **2g**,**h** and tetracyclic compound **2i**. Furthermore, tertiary enamides having both an electron-withdrawing and electron-donating group on the aromatic ketones (**1j–m)** were accepted by the chiral catalytic system, and both high productivity and enantioselection were obtained in the synthesis of **2j–m**. Analogously, a highly enantiopure 2-*tert*-butyl-containg tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one derivative (**2n**) was synthesized in 89% yield from the pivaloyl-bearing tertiary enamide substrate **1n**.

The structures of all products were established on the basis of spectroscopic data. All products gave nearly identical circular dichroism spectra. The absolute configuration was assigned based on that of **2a** and was determined unambiguously by means of single-crystal X-ray crystallography (Figure 3).[21] The facile construction of a tetrahydropyrrolo-[2,1-*a*]isoquinolin-3(2*H*)-one structure that contains two tetrasubstituted stereogenic carbon centers from a one-pot reaction highlights the synthetic power of tandem reactions of tertiary enamides. The formation of single diastereoisomers of highly enantioenriched bicycles (**2**) from the $Cu(OTf)_2$/**L5**-catalyzed tandem cyclization of tertiary enamides (**1**) is worth addressing. The chiral Lewis acid most probably activates the ketonic carbonyl moiety, thus facilitating its reaction with tertiary enamide to form an acyliminium intermediate in an enantioselective manner. Since 2-aryl or 2-*tert*-butyl is much larger than 2-hydroxy in the resulting cyclic acyliminium intermediate, the steric effect exclusively drives the intramolecular attack of an electron-rich dialkoxyphenyl to the *Si* face of acyliminium, thus yielding the product in which two aryls at the 2- and 10b-positions are *cis* oriented.

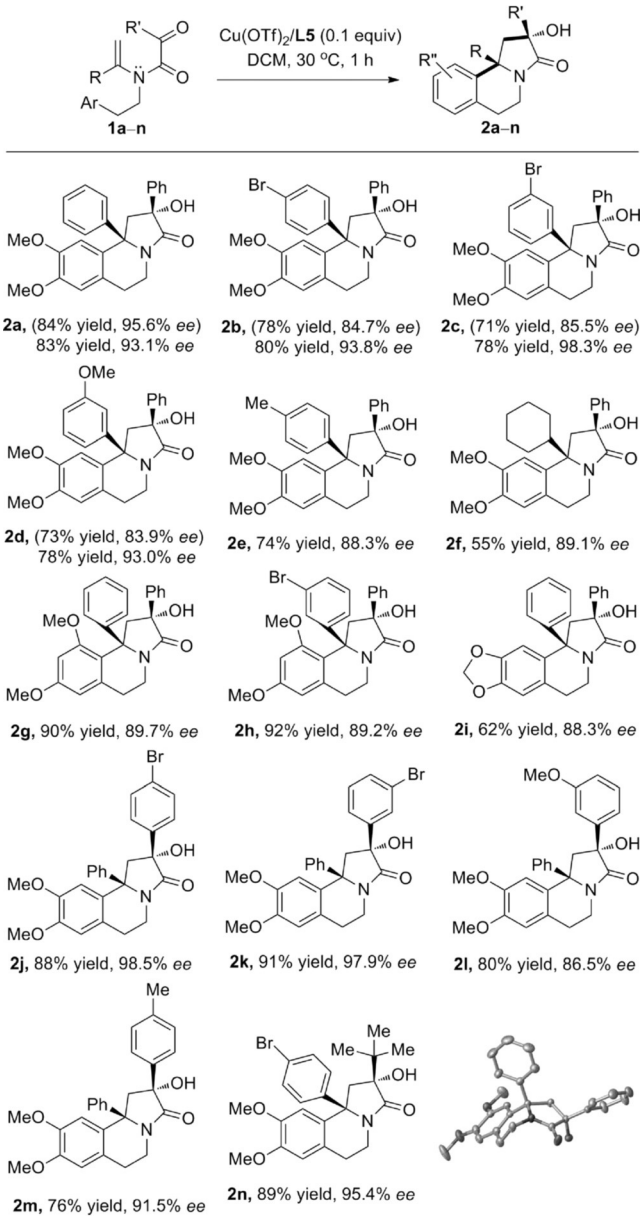


Figure 3. $Cu(OTf)_2$/**L5**-catalyzed enantioselective synthesis of tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one derivatives (**2**) and X-ray structure of **2a**. Yields are those of the isolated products and the *ee* values were determined by chiral HPLC analysis. Chemical yields and enantiomeric excesses given within parentheses are those for reactions catalyzed by the $Cu(OTf)_2$/**L2** complex.

The resulting products not only resemble the structure of tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one alkaloids like (−)-trolline, (+)-oleracein, and erythrosotidienone, but they are also invaluable platforms for the synthesis of diverse (+)-crispine analogues. To demonstrate the utility of the synthetic method, several transformations of **2a** were attempted. As illustrated in Figure 4, treatment of **2a** with

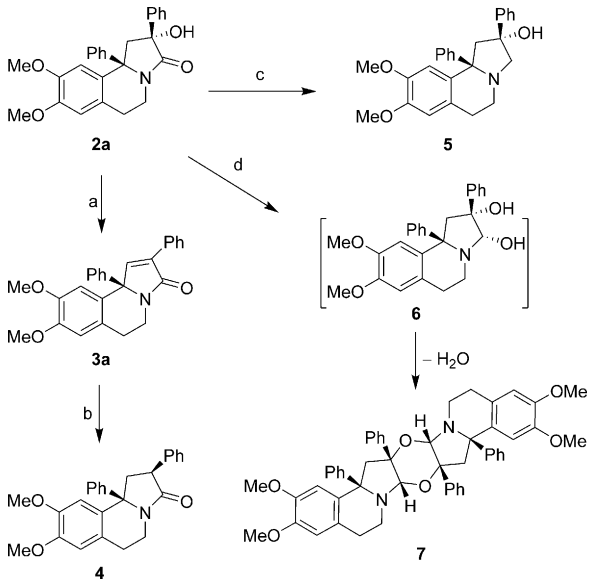


Figure 4. Chemical transformations of **3a**. a) $MeSO_2Cl$, Et_3N, RT, overnight, 99%; b) H_2 (5 mpa), PtO_2, RT, 2 d, 99%, d.r. 9:1; c) $LiAlH_4$ (5 equiv), THF, reflux, 8 h, 82%; d) $LiAlH_4$ (3.5 equiv), THF, 60°C, 4 h, 71%. THF = tetrahydrofuran.

methanesulfonyl chloride and triethylamine afforded, almost quantitatively, the α,β-unsaturated lactam **3a**. Catalytic hydrogenation of **3a**, employing PtO_2 as a catalyst, produced (2S,10*b*R)-8,9-dimethoxy-2,10*b*-diphenyl-1,5,6,10*b*-tetrahydro-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**4**) with a diastereomeric ratio of 9:1. The diastereoselectivity decreased drastically to 5:3 when Pd/C was used as a catalyst. In contrast, reaction of **2a** with 5 equivalents of $LiAlH_4$ in refluxing THF led to the complete reduction of the lactam, thus efficiently yielding the hydroxylated 1,2,3,5,6,10*b*-hexahydropyrrolo[2,1-*a*]isoquinoline product **5**. Interestingly, under milder reduction reaction conditions, the dimeric compound **7** was obtained as the sole product in 71% yield. The formation of a 1,4-dioxane ring-centered fused heterocyclic molecule was most probably a result of the condensation of the diol or N,O-hemiacetal intermediate **6** which was generated from partial reduction of the lactam functionality (Figure 4).

In conclusion, we have developed a novel and efficient strategy for expeditious construction of chiral tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one structures. The protocol comprises a $Cu(OTf)_2$/chiral Pybox complex which catalyzes the enantioselective intramolecular addition of tertiary enamides to ketonic carbonyls with subsequent diastereoselective interception of the resulting acyliminium by a tethered electron-rich aryl moiety, and is reminiscent of asymmetric polyene cyclization processes.[22] The tandem catalytic asymmetric double intramolecular cyclization reactions produce diverse tetrahydropyrrolo[2,1-*a*]isoquinolin-3-(2*H*)-one derivatives in good to excellent yields with high enantiopurity. The products were readily converted into different hexahydropyrrolo[2,1-*a*]isoquinoline derivatives using practical and convenient chemical manipulations. The structure of all these products, which are hardly accessible by other synthetic means, is a key structural motif found in many bioactive alkaloids. The study also demonstrates the power of tandem cyclization reactions of tertiary enamides in the construction of fused heterocyclic rings with multiple quaternary stereogenic centers. Currently, synthesis of erythrina alkaloids based on this methodology is being actively pursued in this laboratory and results will be reported in due course.

Acknowledgments

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Keywords: alkaloids · asymmetric catalysis · copper · cyclizations · synthetic methods

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