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Zinc-Catalyzed Selective Reduction of Cyclic Imides with Hydrosilanes: Synthesis of ω-Hydroxylactams

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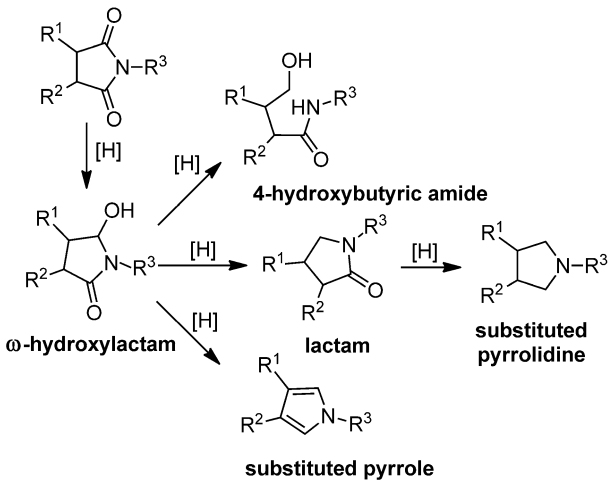
Abstract: Cyclic imides were selectively reduced to the corresponding ω-hydroxylactams in high yields with $(EtO)_3SiH$ (triethoxysilane) or PMHS (polymethylhydrosiloxane) under catalysis of zinc diacetate dehydrate $[Zn(OAc)_2{\cdot}2H_2O]$ (10%) and tetramethylethylenediamine (TMEDA) (10%). This catalytic protocol showed good functional group tolerance as well as excellent regioselectivity for unsymmetrical imides bearing coordinating groups adjacent to the carbonyl.

Keywords: cyclic imides; diamine ligands; hydrosilylation; ω-hydroxylactams; zinc catalysis

Introduction

ω-Hydroxylactams are important structural motifs and versatile building blocks in natural products and pharmaceuticals.[1] They serve as important precursors to *N*-acyliminium ions which are powerful intermediates to form nitrogen-containing heterocycles, particularly in the synthesis of alkaloid natural products.[2] The reduction of cyclic imides is commonly used to access ω-hydroxylactams.[3] The reduction can also provide access to other heterocycles such as lactams,[4] substituted pyrroles,[5] pyrrolidines[6] or 4-hydroxybutyric amides[7] (ring-opening products) which proceed through the ω-hydroxylactam as an intermediate (Scheme 1). Use of typical reducing reagents in the reduction of cyclic imides to ω-hydroxylactams, such as $LiAlH_4$ or $NaBH_4$, always results in undesired by-products, so these reductions require careful temperature control.[2d,8] Hydrogenation of cyclic imides is also accompanied with the formation of over-reduction by-products.[9] Therefore, it is an important synthetic challenge to develop a mild and highly selective method to reduce imides to the desired ω-hydroxylactams.

The chemoselective reduction of multifunctionalized carboxylic acid derivatives is of significant interest and a challenge in organic synthesis.[10] Compared to the typical metal hydride reductants, hydrosilanes are very attractive, because they can be activated under mild conditions, and the chemo- and regioselec-



Scheme 1. The reduction of cyclic imides.

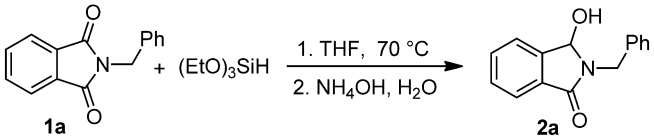
tivities of hydrosilylation can be easily tuned by changing the substituents on the silicon atom and by changing the employed catalysts (fluorides,[11] base,[12] Lewis acids[13] and metal complexes[14]). Moreover, hydrosilanes are readily accessible and easy to handle (less moisture sensitive than metal hydrides).[14]

Recently, the high selectivity and convenience of metal-catalyzed reductions of ketones,[15] amides[16] and esters[17] with hydrosilanes have been realized. However, there are few reports on the selective reduction of imides with hydrosilanes. Reduction of *N*-benzylsuccinimide with Ph_2SiH_2 catalyzed by $RhH(CO)(PPh_3)_3$ gives the corresponding pyrrolidine.[16a] The fluoride-catalyzed hydrosilylation of imides with polymethylhydrosiloxane (PMHS) gives the lactams.[11b] Until now, the selective reduction of imides to ω-hydroxy carboxamides with hydrosilanes has not been reported. Herein, we report an efficient hydrosilylation of cyclic imides to ω-hydroxylactams using convenient zinc catalysts with excellent chemoselectivity and good functional group tolerance.

Results and Discussion

Various metal compounds have been intensively investigated as the catalysts or precatalysts in the hydrosilylation of carbonyl compounds, such as Cu,[18] Ti,[19] Rh,[16a,20] Ru,[16e,17a,21] Ir,[15g,16f,22] Ni,[23] Fe[15d,16b,17c,f,24] and Zn.[14f,16d,17e,25] Almong these catalysts, zinc is of great interest, because of its abundance, low toxicity and good catalytic activity in hydrosilylation reactions of ketones, esters and amides.[6,14f,25] Initially, $Zn(OAc)_2$ was selected for use as the catalyst in the model reduction of *N*-benzylphthalimide (**1a**) (Table 1). When 10% of $Zn(OAc)_2$ and $(EtO)_3SiH$ were used, no reaction occurred in THF at room temperature (entry 1). The reaction temperature was elevated to 70 °C, and then the desired product, 2-benzyl-3-hydroxyphthalimidine (**2a**), was formed in 83% yield after 4 h (entry 2). The result is very promising because reduction of amides to amines was observed with $Zn(OAc)_2$ and $(EtO)_3SiH$.[16d] The formation of amines proceeds through an iminium species followed futher reduction.[16d] Herein, the reduction of phthalimide (**1a**) to ω-hydroxylactams without over-reduction to the lactam is likely due to the additional carbonyl of the imide which decreases the electron-donating nature of the nitrogen atom and inhibits the formation of the iminium species. However, as the reaction time was prolonged to 18 h, the conversion of the imide reached 100%, but the yield of hydroxyphthalimidine (**2a**) did not improve, and an over-reduction product, 2-benzylisoindole, was formed as the major by-product (entry 3). Studies on zinc-catalyzed hydrosilylation of ketone reveal that the coordination of ligands facilitates the formation of monomeric active catalysts.[25] So, the use of ligands in the hydrosilylation was explored. Some simple alcohols and amines were selected as ligands. Addition of 20 mol% of either 2,6-di-*tert*-butylphenol or isopropyl alcohol to the reaction led to increased yields of the hydroxylactam (**2a**), 93% and 92%, respectively (entries 4 and 5). Gratifyingly, when 20 mol% of a simple diethylamine was added, the conversion of *N*-benzylphthalimide (**1a**) was complete in 2.5 h, and nearly exclusive formation of hydroxyphthalimidine (**2a**) was observed (entry 6). In the case of the bulkier secondary amine, $(i\text{-}Pr)_2NH$, complete conversion was observed in only 1 h, with selective formation of hydroxyphthalimidine (**2a**) (entry 7). The conversion of the imide finished in 1.5 h in the presence of Et_3N, while the reaction time was prolonged to 4 h in the case of $(i\text{-}Pr)_2NEt$ (entries 8 and 9). This may be attributed to the higher

Table 1. Optimization of the zinc-catalyzed selective hydrosilane reduction of *N*-benzylphthalimide (**1a**).[a]



Entry	Catalyst	Ligand	Time [h]	Yield[b] [%]
1[c]	$Zn(OAc)_2$	–	18	0
2	$Zn(OAc)_2$	–	4	83
3	$Zn(OAc)_2$	–	18	88
4[d]	$Zn(OAc)_2$	2,6-di-*tert*-butylphenol	4	93
5[d]	$Zn(OAc)_2$	*i*-PrOH	4	92
6[d]	$Zn(OAc)_2$	Et_2NH	2.5	>98
7[d]	$Zn(OAc)_2$	$(i\text{-}Pr)_2NH$	1	>98
8[d]	$Zn(OAc)_2$	Et_3N	1.5	>98
9[d]	$Zn(OAc)_2$	$(i\text{-}Pr)_2NEt$	4	95
10[e]	$Zn(OAc)_2$	TMEDA	1	>98
11[c]	$Ti(OPr)_4$	–	5	72
12	$Cu(OAc)_2$	–	18	0
13	$Fe(OAc)_2$	–	18	0
14[e]	–	TMEDA	18	0
15[e]	$ZnCl_2$	TMEDA	18	<2
16[e]	$ZnBr_2$	TMEDA	18	0
17[e]	$ZnEt_2$	TMEDA	1	>98
18[e]	$Zn(OAc)_2{\cdot}2H_2O$	TMEDA	1	>98
19[f]	$Zn(OAc)_2{\cdot}2H_2O$	TMEDA	7	>98

[a] *Reaction conditions:* *N*-benzylphthalimide (**1a**, 1.0 mmol), $(EtO)_3SiH$ (3.0 equiv., 3.0 mmol), $Zn(OAc)_2$ (10 mol%), THF (2.5 mL), 70 °C.
[b] The yield was determined by ^1H NMR analysis of the crude product.
[c] Room tempertaure.
[d] 0.2 equiv. of ligand (0.2 mmol) were used.
[e] 0.1 equiv. of ligand (0.1 mmol) was used.
[f] $(EtO)_3SiH$ was replaced with PHMS.

steric profile of $(i\text{-Pr})_2$NEt. When 10 mol% TMEDA (tetramethylethylenediamine) was used, the hydrosilylation was completed within one hour and quantitatively gave hydroxyphthalimidine (**2a**) (entry 10). It was taken into consideration that the bidendate diamine ligand is more beneficial for the formation of stable monomeric active catalyst, so TMEDA was used as the ligand in the hydrosilylation for the further exploration.

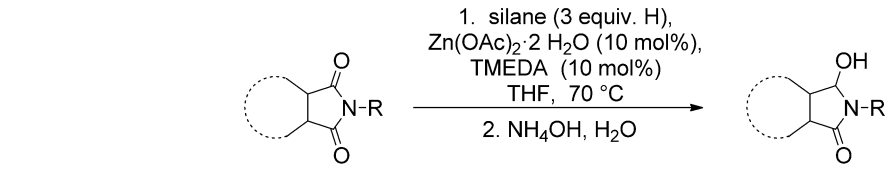
On replacing $Zn(OAc)_2$ with $Ti(OPr)_4$ as the catalyst, the over-reduction occurred quickly even at room temperature. The formation of hydroxyphthalimidine (**2a**) was accompanied with 17% of 2-benzylisoindole and 10% of *N*-benzylphthalimidine (entry 11). In addition, $Cu(OAc)_2$ and $Fe(OAc)_2$ were completely inactive in this reaction (entries 12 and 13). These results indicated the zinc catalyst was essential for the chemselective hydrosilylation of the imide. As expected, the hydrosilylation of the imide (**1a**) did not occur in the absence of $Zn(OAc)_2$ (entry 14). Replacement of $Zn(OAc)_2$ with zinc halides, resulted in no or very low activity. Although $ZnEt_2$ was also a good catalyst for the hydrosilylation, it is flammable and not stable at ambient temperature. To our delight, when the cheaper and readily available $Zn(OAc)_2{\cdot}2H_2O$ was used as the catalyst, the fast reaction rate and high selectivity for the hydrosilylation were still observed (entry 15). In addition, the catalyst system, $Zn(OAc)_2{\cdot}2H_2O$ and TMEDA, shows high activity and chemoselectivity in various solvents, such as dioxane, DME (dimethoxyethane), toluene, and DCE (1,2-dichloroethane) (see the Supporting Information). However, omission of the ligand resulted in the need for a longer reaction time in poor coordinating solvents such as DCE and toluene, and an induction period of 9 h was observed. This observation reveals that the coordination of solvent may promote the formation of monomeric active catalysts. We are pleased to find that the use of PMHS, a safe and inexpensive silane, also provided the ω-hydroxylactams in quantitative yield after 7 h (entry 19), and the excess hydrosilane did not result in the formation of over-reduction product (see the Supporting Information).

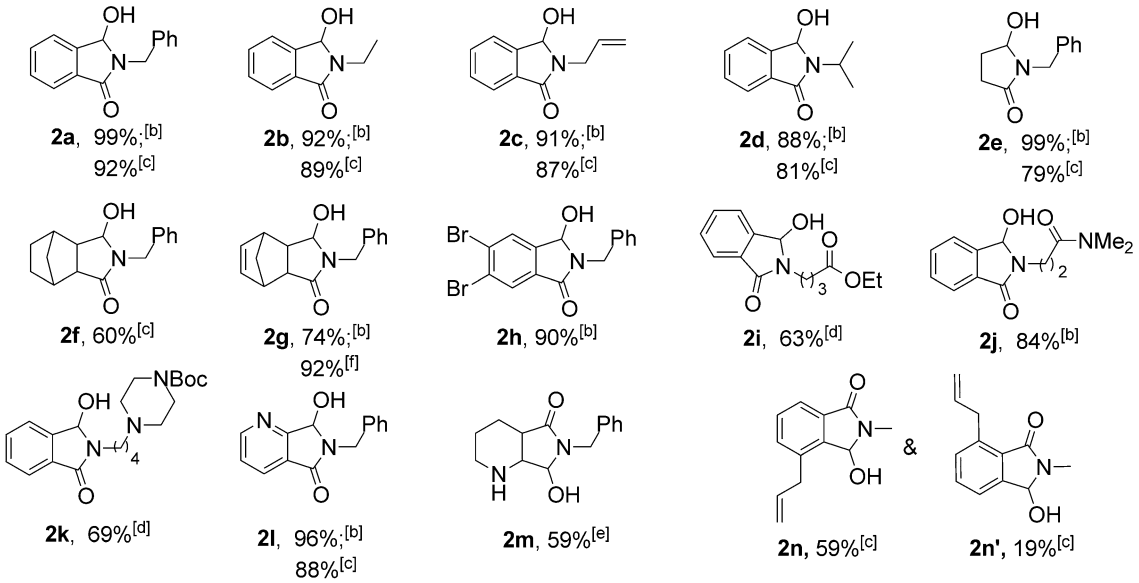
The scope of zinc-catalyzed selective hydrosilane reduction of imides was then explored. As shown in Table 2, various *N*-substituted imides (**1**) were smoothly reduced to the corresponding ω-hydroxylactams (**2**), without the formation of over-reduction byproducts. Aromatic, aliphatic, heterocyclic and polycyclic imides were reduced to the corresponding ω-hydroxylactams in good yield either with $(EtO)_3SiH$ or PMHS. *N*-Benzylsuccinimide (**1e**) was reduced to 5-hydroxy-1-(phenylmethyl)-2-pyrrolidinone (**2e**) in 99% yield which was purified by simple recrystallization. *endo*-*N*-Benzylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide was reduced to the ω-hydroxylactam (**2g**) in 74% yield, and the yield was increased to 92% when $ZnEt_2$ was used as the catalyst. The substituents at the nitrogen atom did not impact on the hydrosilylation. The reduction of bulkier *N*-isopropylphthalimidine afforded the corresponding product in 88% yield. Moreover, the catalytic system showed good tolerance for functional groups such as halogen, alkene, amide, ester, and carbamic ester. Reaction of *N*-benzyl-5,6-dibromophthalimide (**1h**) proceeded smoothly to give the desired product in 90% yield without the formation of the dehalogenated product. Although the hydrosilylation system, $(EtO)_3SiH$ and 10% of $Zn(OAc)_2$, is efficient for the reduction of amides, *N*,*N*-dimethyl-1,3-dioxo-2-isoindolinepropionamide (**1j**) was selectively reduced to afford the corresponding ω-hydroxylactams (**2j**) without the reduction of the amide group. In addition, the unsymmetrical imides were reduced with high regioselectivity in this catalytic protocol. The hydrosilylation of *N*-benzyl-2,3-pyridinedicarboximide and *N*-benzyl-5,7-dioxooctahydro pyrrolo[3,4-*b*]pyridine selectively afforded the ω-hydroxylactams **2l** in 96% yield and **2m** in 59% yield, respectively. In these cases, the carbonyl with a coordinating group at the adjacent position was reduced selectively. The selectivity likely resulted from the coordination of the heteroatom or double bond with zinc, leading to the reduction of the adjacent carbonyl. Furthermore, the reaction was easily scaled up to a 5.0 g scale of **1a**, and 4.7 g of **2a** were obtained by simple recrystallization of the crude product.

Cationic π-cyclization of *N*-acyliminium ions with alkene or aromatic ring nucleophiles is a powerful method to form indolizidine alkaloids which exhibit attractive biological activity.[2b] The indolizidine alkaloid, 7-(formyloxy)hexahydro-3(2*H*)-indolizinone (**3**), could be formed with a high degree of stereochemical control (>90%) by the cyclization of ω-hydroxylactam (**2o**) in formic acid at room temperature.[1g,2b,26] The important intermediate, 1-(3-buten-1-yl)-5-hydroxy-2-pyrrolidinone (**2o**), has been synthesized previously in 76% yield by the reduction of the corresponding imide with $NaBH_4$ at 0 °C. Encouraged by the above results, the reduction of *N*-(3-butenyl)succinimide (**1o**) was explored with our catalytic hydrosilylation system. Under the optimized conditions, **2o** was isolated in 86% yield, and the crude product of hydrosilylation was used directly without further purification in the cyclization to furnish the desired indolizidine (**3**) in 86% yield and 95% diastereoselectivity which results from an energetically favorable boat-like transition state (Scheme 2).[1g,2b,26]

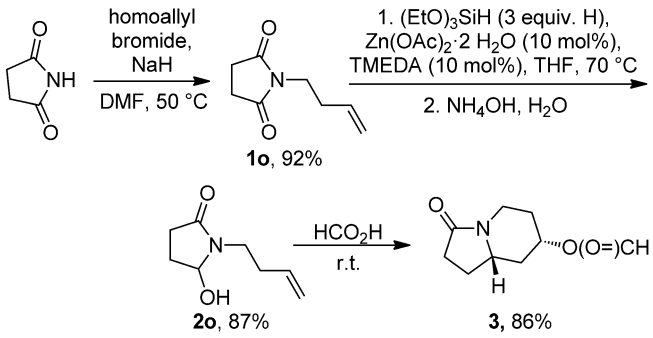
Furthermore, we utilized the zinc-catalyzed hydrosilylation of imides to synthesize the racemic crispine A which was isolated from the Chinese folk medicine, *Carduus crispus*. The useful biological activities and the interesting structure of the isoquinoline alkaloids

Table 2. Zinc-catalyzed selective hydrosilane reduction of *N*-benzylimides (**1**).[a]

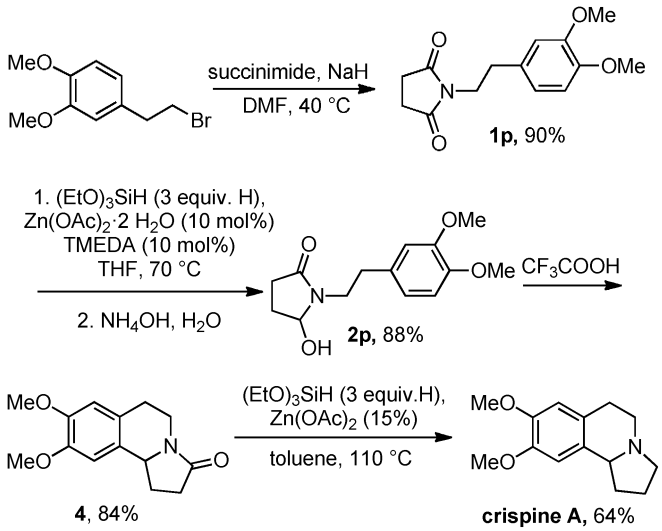




[a] *Reaction conditions:* imide (**1**, 1.0 mmol), silane (3.0 equiv., 3.0 mmol), $Zn(OAc)_2{\cdot}2H_2O$ (10 mol%), TMEDA (10 mol%), THF (2.5 mL), 70 °C, isolated yield.
[b] $(EtO)_3SiH$ (3.0 equiv., 3.0 mmol).
[c] PHMS (3.0 equiv., 3.0 mmol).
[d] $(EtO)_3SiH$ (2.0 equiv., 2.0 mmol).
[e] $(EtO)_3SiH$ (4.0 equiv., 4.0 mmol).
[f] $ZnEt_2$ (10 mol%).



Scheme 2. The synthetic route to 7-(formyloxy)hexahydro-*trans*-3(2*H*)-indolizinone.



Scheme 3. The synthetic route to racemic crispine A.

led to a tremendous interest in the development of efficient synthetic routes.[27] The corresponding *N*-substituted imide (**1p**) was obtained by the nucleophilic substitution of 2-(3,4-dimethoxyphenyl)ethyl bromide with succinimide in 90% yield, and then the reduction of the imide (**1p**) selectively gave the ω-hydroxylactam (**2p**) in 88% yield in our catalytic hydrosilylation system. Subsequent cyclization with trifluoroacetic acid gave **4** in 84% yield. Finally, the reduction of **4** by zinc-catalyzed hydrosilylation was successfully per-

formed using toluene as the solvent and provided a 64% yield of racemic crispine A (Scheme 3).

Conclusions

In summary, we have developed a readily accessible zinc-catalyzed selective hydrosilylation of imides to access ω-hydroxylactams. The combination of $Zn(OAc)_2{\cdot}2H_2O$ and TMEDA was found to be a competent catalyst system to utilize the inexpensive silanes, $(EtO)_3SiH$ or PMHS, in the reduction of aromatic, aliphatic, and heterocyclic imides to corresponding ω-hydroxylactams in good to excellent yields. This catalytic protocol showed good functional group tolerance as well as excellent regioselectivity for unsymmetrical imides bearing coordinating groups adjacent to the carbonyl. Moreover, the products formed in this method were found to be useful synthetic intermediates towards *N*-acyliminium ions in the total synthesis of the indolizidine and isoquinoline alkaloids.

Experimental Section

Typical Procedure for the Hydrosilylation of Cyclic Imides (1) to the ω-Hydroxylactams (2)

To the mixture of $Zn(OAc)_2{\cdot}2H_2O$ (22.4 mg, 0.1 mmol) and TMEDA (11.6 mg, 0.1 mmol) in THF (1.0 mL), was added $(EtO)_3SiH$ (492.9 mg, 3.0 mmol) or PMHS (200.6 mg, 3.0 equiv. based on H) slowly under an atmosphere of nitrogen. Then the solution of the cyclic imides (1.0 mmol) in THF (1.5 mL) was added to the mixture. The reaction mixture was refluxed under an atmosphere of nitrogen. After the imide was consumed completely (detected by TLC), the reaction mixture was cooled to room temperature, and then quenched by adding CH_3OH (1 mL) and $NH_3{\cdot}H_2O$ (1 mL). The mixture was filtered and the solid was washed with THF (5 mL × 2). After removing the solvent under vacuum, the residue was purified by column chromatography to give the product.

2-Benzyl-3-hydroxyisoindolin-1-one (2a):[28] White solid; yield: 236.9 mg (99%); mp 141.7–143.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.77 (m, 1H), 7.58–7.56 (m, 2H), 7.52–7.48 (m, 1H), 7.33–7.25 (m, 5H), 5.63 (d, J = 11.6 Hz, 1H), 5.03 (d, J = 14.8 Hz, 1H), 4.35 (d, J = 14.8 Hz, 1H), 2.63 (d, J = 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 144.2, 136.8, 132.5, 131.2, 129.8, 128.8, 128.5, 127.7, 123.6, 123.4, 81.1, 42.6.

2-Ethyl-3-hydroxyisoindolin-1-one (2b):[3c] White solid; yield: 163.0 mg (92%); mp 105.0–107.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 1H), 7.62–7.70 (m, 1H), 7.57 (td, J = 7.2 Hz, 1.2 Hz, 1H), 7.47 (td, J_1 = 7.2, 1.2 Hz, 1H), 5.79 (d, J = 12.0 Hz, 1H), 3.72–3.63 (m, 1H), 3.45–3.36 (m, 1H), 2.74 (d, J = 12.0 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 144.1, 132.1, 131.4, 129.5, 123.3, 122.9, 81.1, 33.8, 13.5.

2-Allyl-3-hydroxyisoindolin-1-one (2c):[29] White solid; yield: 172.2 mg (91%); mp 86.8–89.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 1H), 7.63–7.61 (m, 1H), 7.58 (td, J = 7.2 Hz,1.2 Hz, 1H), 7.48 (td, J = 7.2 Hz, 1.2 Hz, 1H), 5.82–5.75 (m, 2H), 5.24–5.18 (m, 2H), 4.28–4.24 (m, 1H), 3.83 (dd, J = 15.2 Hz, 7.6 Hz, 1H), 3.02 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 144.1, 132.5, 132.4, 131.2, 129.7, 123.5, 123.2, 118.0, 81.2, 41.4.

2-Isopropyl-3-hydroxyisoindolin-1-one (2d):[30] White solid; yield: 104.9 mg (88%); mp 95.4–97.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.71 (m, 1H), 7.56–7.53 (m, 2H), 7.50–7.46 (m, 1H), 5.91 (d, J = 11.6 Hz, 1H), 4.45–4.38 (m, 1H), 2.43 (d, J = 11.6 Hz, 1H), 1.43 (d, J = 4.0 Hz, 3H), 1.41 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 144.1, 131.9, 131.8, 129.4, 123.0, 122.9, 81.3, 43.9, 21.9, 20.1.

1-Benzyl-5-hydroxypyrrolidin-2-one (2e):[31] White solid; yield: 189.3 mg (99%); mp 108.3–110.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5H), 5.09 (td, J_1 = 3.2 Hz, 1.6 Hz, 1H), 4.83 (d, J = 14.8 Hz, 1H), 4.23 (d, J = 14.8 Hz, 1H), 2.68–2.60 (m, 1H), 2.43–2.27 (m, 3H), 1.93–1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 136.5, 128.7, 128.3, 127.6, 82.4, 43.3, 29.1, 28.0.

2-Benzyl-3-hydroxyoctahydro-1*H*-4,7-methanoisoindol-1-one (2f): White solid; yield: 154.4 mg (60%); mp 148.5–157.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 5H), 5.06 (t, J = 8.0 Hz, 1H), 4.80 (d, J = 14.4 Hz, 1H), 4.25 (d, J = 14.4 Hz, 1H), 2.83–2.80 (m, 1H), 2.68–2.65 (m, 2H), 2.48 (br, 1H), 2.39 (d, J = 8.0 Hz, 1H), 1.78–1.72 (m, 1H), 1.62–1.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 136.9, 128.7, 128.6, 127.6, 81.7, 48.6, 44.1, 43.5, 41.7, 40.1, 38.8, 25.3, 24.3; HR-MS-ESI: m/z = 258.1482, calculated for $C_{16}H_{19}NO_2$ $(M+H)^+$: 258.1494.

2-Benzyl-3-hydroxyhexahydro-1*H*-4,7-methano-isoindol-1-one (2g):[32] White solid; yield: 166.7 mg (74%); mp 119.5–126.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 3H), 7.25–7.23 (m, 2H), 6.26–6.21 (m, 2H), 5.00 (dd, J = 10.0 Hz, 8.0 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 4.09 (d, J = 14.8 Hz, 1H), 3.34–3.32 (m, 1H), 3.19 (dd, J = 8.8 Hz, 4.4 Hz, 1H), 3.08–3.07 (m, 1H), 3.04–2.99 (m, 1H), 1.83–1.80 (m, 1H), 1.62 (dt, J = 8.4 Hz, 0.8 Hz, 1H), 1.45–1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.6, 136.8, 135.9, 134.5, 128.7, 128.5, 127.6, 81.9, 52.3, 49.9, 45.9, 44.7, 43.4, 43.2.

2-benzyl-5,6-dibromo-3-hydroxyisoindolin-1-one (2h): Pale yellow solid; yield: 358.2 mg (90%); mp 217.6–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.99 (s, 1H), 7.98 (s, 1H), 7.33–7.23 (m, 5H), 6.91 (d, J = 8.8 Hz, 1H), 5.65 (d, J = 8.8 Hz, 1H), 4.86 (d, J = 15.2 Hz, 1H), 4.34 (d, J = 15.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 145.4, 137.3, 132.5, 129.3, 128.5, 128.0, 127.8, 127.4, 127.2, 125.2, 79.7, 42.4; HR-MS-ESI: m/z = 395.9263, calculated for $C_{15}H_{11}Br_2NO_2$ $(M+H)^+$: 395.9235.

Ethyl 4-(1-hydroxy-3-oxo-1*H*-isoindol-2-yl)butanoate (2i): Pale yellow liquid; yield: 165.9 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.52 (m, 3H), 7.43 (td, J = 7.2 Hz, 1.2 Hz, 1H), 5.76 (d, J = 9.6 Hz, 1H), 4.38 (d, J = 10.8 Hz, 1H), 3.97 (q, J = 7.2 Hz, 2H), 3.47 (t, J = 6.8 Hz, 2H), 2.40–2.27 (m, 2H), 2.00–1.90 (m, 2H), 1.64 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 167.6, 144.0, 132.1, 131.2, 129.4, 123.2, 122.9, 81.7, 60.5, 38.6, 31.6,

23.5, 14.0. HR-MS-ESI: m/z = 286.1062, calculated for $C_{14}H_{17}NO_4$ $(M+Na)^+$: 286.1055.

***N*,*N*-Dimethyl 3-(1-hydroxy-3-oxo-1*H*-isoindol-2-yl)propanamide (2j):** White solid; yielkd: 208.4 mg (84%); mp 112.1–115.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.74 (m, 1H), 7.59–7.53 (m, 2H), 7.46 (td, J = 7.2 Hz, 1.6 Hz, 1H), 6.20 (d, J = 4.4 Hz, 1H), 5.88 (d, J = 4.4 Hz, 1H), 3.98–3.85 (m, 2H), 3.01 (s, 3H), 2.96 (s, 3H), 2.94–2.89 (m, 1H), 2.68–2.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 167.9, 144.1, 132.1, 131.6, 129.3, 123.3, 122.9, 82.6, 37.2, 35.9, 35.6, 32.7; HR-MS-ESI: m/z = 271.1060, calculated for $C_{13}H_{16}N_2O_3$ $(M+Na)^+$: 271.1059.

***tert*-Butyl 4-[4-(1-hydroxy-3-oxo-1*H*-isoindol-2-yl)but-1-yl]piperazine-1-carboxylate (2k):** White solid; yield: 367.4 mg (69%); mp 108.4–111.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.73 (m, 1H), 7.61–7.54 (m, 2H), 7.48 (td, J = 7.2 Hz, 1.2 Hz, 1H), 5.80 (s, 1H), 3.86–3.79 (m, 1H), 3.52–3.46 (m, 1H), 3.26 (t, J = 4.8 Hz, 4H), 2.40–2.27 (m, 3H), 2.21–2.15 (m, 1H), 2.05–2.00 (m, 3H), 1.69–1.60 (m, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 154.6, 144.6, 132.1, 131.6, 129.5, 123.2, 123.0, 82.3, 79.8, 57.5, 52.6, 43.4, 42.5, 39.6, 28.4, 26.0, 23.8; HR-MS-ESI: m/z = 390.2379, calculated for $C_{21}H_{31}N_3O_4$ $(M+H)^+$: 390.2393.

6,7-Dihydro-7-hydroxy-6-(phenylmethyl)-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (2l):[33] Pale yellow solid; yield: 230.6 mg (96%); mp 184.3–193.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.78 (dd, J = 4.8 Hz, 0.8 Hz, 1H), 8.11 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.57 (dd, J = 7.6 Hz, 4.8 Hz, 1H), 7.34–7.32 (m, 4H), 7.30–7.25 (m, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.63 (d, J = 8.4 Hz, 1H), 4.93 (d, J = 15.2 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.8, 163.9, 152.8, 137.5, 131.2, 128.5, 127.8, 127.2, 125.2, 124.7, 80.8, 42.2.

***cis*-8-Benzyl-7-hydroxy-9-dioxo-2,8-diazabicyclo[4.3.0]nonane (2m):** Pale yellow oil; yield: 145.3 mg (59%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 5H), 4.75 (d, J = 15.2 Hz, 1H), 4.55 (s, 1H), 4.17 (d, J = 15.2 Hz, 1H), 3.62 (br, 2H), 3.23 (d, J = 5.4 Hz, 1H), 2.75–2.69 (m, 2H), 2.48–2.42 (m, 1H), 2.10–2.06 (m, 1H), 1.65–1.56 (m, 1H), 1.48–1.44 (m, 1H), 1.34–1.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 136.7, 128.7, 128.1, 127.5, 85.3, 58.4, 43.9, 43.4, 38.5, 23.3, 21.4; HR-MS-ESI: m/z = 245.1292, calculated for $C_{14}H_{16}N_2O_2$ $(M+H)^+$: 245.1290.

2-Benzyl-3-hydroxy-4-allylisoindol-1-one (2n): White solid; yield: 120.0 mg (59%); mp 101.8–105.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 2H), 7.24–7.22 (m, 1H), 5.99–5.89 (m, 1H), 5.58 (d, J = 12.0 Hz, 1H), 5.06–5.04 (m, 1H), 5.02–5.01 (m, 1H), 3.84–3.57 (m, 2H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 144.7, 139.3, 136.6, 132.1, 130.7, 127.8, 121.3, 116.3, 82.9, 34.5, 26.2; HR-MS-ESI: m/z = 204.1021, calculated for $C_{12}H_{13}NO_2$ $(M+H)^+$: 204.1025.

2-Benzyl-3-hydroxy-7-allylisoindol-1-one (2n′): White solid; yield: 38.6 mg (19%); mp 106.6–113.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.42 (m, 1H), 7.39–7.34 (m, 2H), 6.05–5.97 (m, 1H), 5.66 (d, J = 11.2 Hz, 1H), 5.14–5.08 (m, 2H), 3.74–3.53 (m, 2H), 3.40 (d, J = 11.2 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 141.6, 136.5, 136.1, 133.1, 131.6, 130.0, 121.2, 116.8, 83.2, 35.8, 26.1; HR-MS-ESI: m/z = 204.1024, calculated for $C_{12}H_{13}NO_2$ $(M+H)^+$: 204.1025.

Experimental Procedure for the Synthesis and Characterization Data of *trans*-7-(Formyloxy)-hexahydro-3(2*H*)-indolizinone

***N*-(3-Butenyl)succinimide (1o):**[34] To a solution of succinimide (5.0 g, 50.5 mmol) in DMF, was added sodium hydride (1.5 g, 60.5 mmol) carefully. After stirring for 1 h at room temperature, 4-bromo-1-butene (8.17 g, 60.5 mmol) was added to the reaction mixturewhich was then stirred at 50 °C for 20 h. After DMF was removed under vacuum, water (30 mL) was added to the residue, and the mixture extracted with CH_2Cl_2 (50 mL × 3). The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (PE/EA = 5/1) to give **1o** as a pale yellow oil; yield: 7.1 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.78–5.67 (m, 1H), 5.07–5.01 (m, 2H), 3.59 (t, J = 7.2 Hz, 2H), 2.69 (s, 4H), 2.37–2.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 134.2, 116.8, 37.3, 31.5, 27.7.

1-(3-Buten-1-yl)-5-hydroxy-2-pyrrolidinone (2o):[1g] To the mixture of $Zn(OAc)_2$ (128.5 mg, 0.7 mmol) and TMEDA (75.9 mg, 0.7 mmol) in THF, was added $(EtO)_3SiH$ (3.2 g, 19.5 mmol) slowly under an atmosphere of nitrogen. Then **1o** (1.0 g, 6.5 mmol) was added to the mixture. The reaction mixture was refluxed for 22 h under an atmosphere of nitrogen. The reaction was quenched by adding CH_3OH (6 mL) and $NH_3{\cdot}H_2O$ (9 mL). The mixture was filtered, and the solid was washed with THF (10 mL). After removing the solvent under vacuum, the residue was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried over Na_2SO_4. After removing the solvent under vacuum, the crude product (**2o**) was obtained as a pale yellow oil; yield: 0.9 g (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77–5.68 (m, 1H), 5.21–5.17 (m, 1H), 5.07–4.99 (m, 2H), 4.79–4.62 (m, 1H), 3.56–3.49 (m, 1H), 3.23–3.16 (m, 1H), 2.53–2.47 (m, 1H), 2.31–2.24 (m, 4H), 1.91–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 135.3, 117.0, 83.3, 39.3, 32.1, 29.1, 28.3.

***trans*-7-(Formyloxy)hexahydro-3(2*H*)-indolizinone (3):**[1g] Pyrrolidinone **2o** (1.0 g, 6.4 mmol) was added to formic acid, and the reaction mixture was stirred for 12 h at room temperature. After the formic acid was removed under vacuum, the residue was added with water (8 mL) and extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried over Na_2SO_4. After removing the solvent under vacuum, the residue was purified by column chromatography (DCM/CH_3OH = 20/1) to give **3** as a yellow oil; yield: 1.0 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 5.03–4.96 (m, 1H), 4.23–4.18 (m, 1H), 3.61–3.54 (m, 1H), 2.73 (td, J_1 = 13.6 Hz, 3.2 Hz, 1H), 2.42–2.38 (m, 2H), 2.27–2.22 (m, 2H), 2.05–2.00 (m, 1H), 1.70–1.61 (m, 1H), 1.54–1.44 (m, 1H), 1.35–1.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 160.4, 70.3, 55.2, 38.7, 37.4, 30.3, 30.0, 24.6.

Experimental Procedure for the Synthesis and Characterization Data of Racemic Crispine A

***N*-(3,4-Dimethoxyphenethyl)succinimide (1p):**[35] To a solution of succinimide (5.0 g, 50.5 mmol) in DMF, was added sodium hydride (1.5 g, 60.5 mmol) carefully. After stirring for 1 h at r. t., the reaction mixture was added with 4-(2-bromoethyl)-1,2-dimethoxybenzene (14.8 g, 60.5 mmol) and stirred at 40 °C for 3 h. After DMF was removed under

vacuum, water (30 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM/EA = 2/1) to give **1p** as a white solid; yield: 12.3 g (93%); mp 123.7–125.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80–6.75 (m, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.75–3.71 (m, 2H), 2.85–2.81 (m, 2H), 2.66 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 149.0, 147.8, 130.3, 120.9, 112.0, 111.3, 56.0, 40.1, 33.2, 28.2.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-5-hydroxy-2-pyrrolidinone (2p):[36] To the mixture of $Zn(OAc)_2{\cdot}2H_2O$ (87.8 mg, 0.4 mmol) and TMEDA (46.5 mg, 0.4 mmol) in THF, was added $(EtO)_3SiH$ (1.9 g, 11.4 mmol) slowly under an atmosphere of nitrogen. Then **1p** (1.0 g, 3.8 mmol) was added to the mixture.The reaction mixture was refluxed for 22 h under an atmosphere of nitrogen. The reaction was quenched by adding CH_3OH (4 mL) and $NH_3{\cdot}H_2O$ (6 mL). The mixture was filtered, and the solid was washed with THF (10 mL). After removing the solvent under vacuum, the residue was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried over Na_2SO_4. After removing the solvent under vacuum, the resdiue was purified by column chromatography DCM/EA = 5/1) to give the product (**2p**) as a white solid; yield: 0.9 g (88%); mp 107.9–111.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80–6.73 (m, 3H), 4.98–4.95 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.73–3.66 (m, 1H), 3.45–3.38 (m, 1H), 2.86–2.82 (m, 3H), 2.57–2.50 (m, 1H), 2.29–2.23 (m, 2H), 1.85–1.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 148.9, 147.6, 131.4, 120.7, 112.0, 111.3, 83.6, 55.9, 41.7, 33.6, 29.0, 28.3.

1,5,6,10b-Tetrahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (4):[27c] Pyrrolidinone **2p** (1.0 g, 3.8 mmol) was added to trifluoroacetic acid (4.7 g, 41.5 mmol), and the reaction mixture was stirred for 2 h at room temperature, after which saturated sodium carbonate was added into the reaction mixture. Then the mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (DCM/CH_3OH = 20/1) to give **4** as a green solid; yield: 0.8 g (84%); mp 99.5–102.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (s, 1H), 6,54 (s, 1H), 4.69 (t, J = 7.6 Hz, 1H), 4.27 (dd, J = 12.8 Hz, 4.4 Hz, 1H), 3.83 (d, J = 4.0 Hz, 6H), 2.97 (dt, J = 11.6 Hz, 4.4 Hz, 1H), 2.89–2.80 (m, 1H), 2.67–2.39 (m, 4H), 1.84–1.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2, 148.1, 147.8, 129.3, 125.5, 111.6, 107.6, 56.6, 56.1, 55.9, 37.1, 31.8, 28.1, 27.8.

Racemic crispine A:[27c] To the mixture of $Zn(OAc)_2$ (111.3 mg, 0.6 mmol) in toluene, was added $(EtO)_3SiH$ (2.0 g, 12.1 mmol) slowly under an atmosphere of nitrogen, and then **4** (1.0 g, 4.0 mmol) was added to the mixture. The reaction mixture was stirred at 70 °C for 24 h. The reaction was quenched by adding CH_3OH (4 mL) and $NH_3{\cdot}H_2O$ (6 mL). The mixture was filtered, and the solid was washed with THF (10 mL). After removing the solvent under vacuum, the residue was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was dried over Na_2SO_4. After removing the solvent under vacuum, the crude material was purified by column chromatography (EA/CH_3OH = 5/1) to give the product as a brown solid; yield: 0.6 g (64%); mp 89.7–92.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1H), 6.56 (s, 1H), 3.84 (s, 6H), 3.51 (t, J = 8.0 Hz, 1H), 3.19–3.14 (m, 1H), 3.09–2.98 (m, 2H), 2.77–2.63 (m, 4H), 2.38–2.30 (m, 1H), 1.97–1.85 (m, 3H), 1.78–1.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 147.2, 130.4, 125.9, 111.2, 108.8, 62.6, 55.9, 55.8, 53.0, 48.0, 30.6, 29.6, 27.7, 22.2.

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