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Merging Asymmetric Henry Reaction with Organocatalytic Cascade Reaction for the Construction of a Chiral Indolizidine Alkaloid Skeleton

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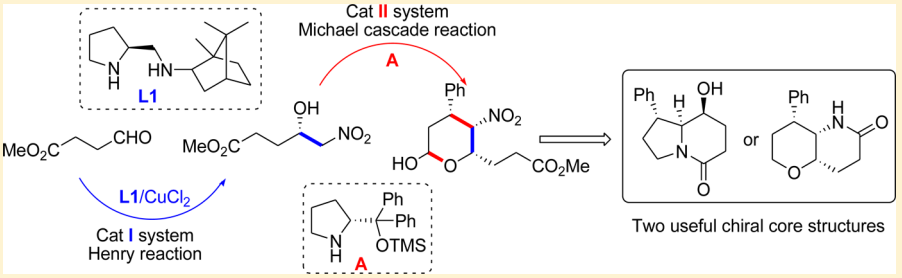
Supporting Information



ABSTRACT: A sequential reaction combining the copper-catalyzed asymmetric Henry reaction with the organocatalytic Michael addition−hemiacetalization cascade reaction was developed. The C_1-symmetric chiral diamine **L1**−copper complex was responsible for the first highly enantioselective Henry reaction, while diphenylprolinol silyl ether **A** acted as effective organocatalyst for the second cascade reaction between chiral *β*-nitro alcohol and *α*,*β*-unsaturated aldehydes. Via rational design and combination of the two independent catalytic systems, good yields and excellent enantioselectivities and diastereoselectivities were achieved for a broad substrate scope under mild reaction conditions. The synthetic utility of this sequential catalytic asymmetric cascade reaction was demonstrated as an alternative and straightforward stereoselective synthesis strategy for chiral indolizidine alkaloid and its analogues.

INTRODUCTION

Indolizidine alkaloids can be found in a large family of important naturally occurring molecules which have wide biological, pharmacological, and medicinal applications.[1−4] The core structure of this bicyclic system is symbolized as fused five- and six-numbered rings bearing a bridgehead tertiary amine nitrogen atom (Figure 1).[1−4] For instance, coniceine,[5] containing the simplest unsubstituted skeleton, was obtained from the hemlock alkaloid coniine. An important class is plant-derived polyhydroxylated indolizidines, such as swainsonine[6,7] and lentiginosinee,[8,9] which served as selective glycosidase inhibitors exhibiting diverse biological activities. 5-Indolizidione[10−12] had been used as a valuable intermediate for the assembly of many kinds of different indolizidine alkaloids. Esculeoside B[13] as a novel steroidal alkaloid glycoside was isolated from the red color-type tomato which was further identified having anticancer activity. As a consequence, tremendous effort has been devoted to the development of various synthetic methods for this kind of privileged fragment.[14−17] Although great success has been achieved for the construction of these useful alkaloids, there are some limitations for most of the established strategies. For example, the starting materials were tedious and restricted to natural amino acids,[18−27] sugars,[28−33] or other chiral synthons,[34−44] and chiral auxiliaries were usually required for chiral induction.[45−48] In particular, the reported examples always suffered from long synthesis routes with low efficiency and atom economy. Very recently, Shenvi and co-workers illustrated an impressive chemoselective hydroamination of simple

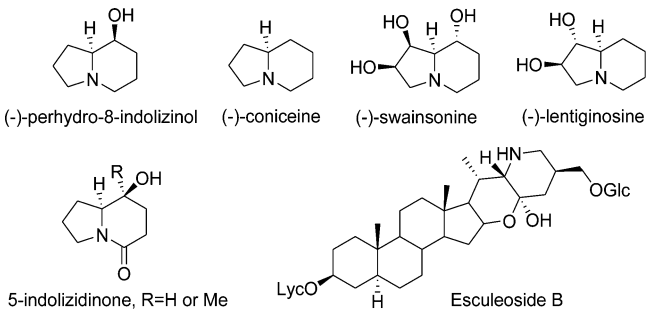


Figure 1. Selected examples of indolizidine alkaloids.

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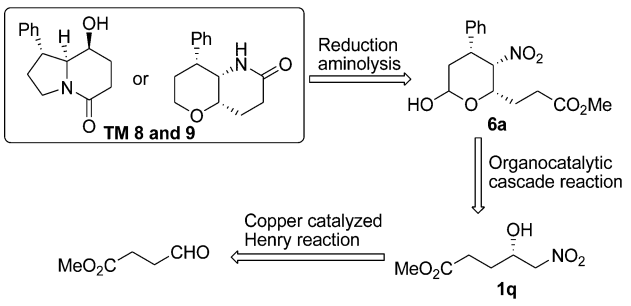
unsaturated amines to prepare indolizidines with excellent diastereocontrol.[49,50] However, there were only few examples involved catalytic enantioselective approaches.[51−59] Thus, asymmetric catalytic step-economical access to indolizidine alkaloids bearing multiple chiral centers is highly desirable.

For the past decade, the asymmetric organocatalytic cascade reaction has emerged as one of the most promising approaches for natural product total syntheses.[60−68] Nitro compounds bearing another reactive moiety such as hydroxyl, amine, or carbonyl have been well-coupled in the tandem cyclization with various enals, which were always initiated by nucleophlic Michael addition.[69−81] Recently, Hayashi and our group have independently demonstrated that nitroethanol,[79] racemic β-substituted β-nitroethanols,[80] as well as 1-nitromethylcycloalkanol[81] can serve as suitable partners for the organocatalytic asymmetric Michael addition−hemiacetalization cascade reaction of α,β-unsaturated aldehydes, providing polysubstituted chiral tetrahydropyrans which can be further transformed into vast and assorted useful core architectures by various derivations. Although excellent enantioselectivities were achieved, diastereoselectivities were rather moderate. Considering asymmetric Henry reactions can deliver chiral β-nitro alcohol adducts, we envisioned that these chiral β-nitro alcohols could act as potential starting materials for the above cascade reaction. With the assistance of the adjacent chiral center of β-nitro alcohol, the diastereoselectivity may be improved. Recently, we have developed a series of C_1-symmetric chiral diamine ligands and found successful application in highly enantioselective copper-catalyzed Henry reactions[82−86] and organocatalytic Michael additions.[87,88] According to retrosynthetic analysis illustrated in Scheme 1, we realized a possible

Scheme 1. Retrosynthetic Analysis for Indolizidine Alkaloid and Its Homologues



construction of chiral fused bicyclic indolizidine alkaloid via sequential asymmetric Henry reaction and Michael addition−hemiacetalization cascade process.

RESULTS AND DISCUSSION

Toward this end, (*S*)-2-nitro-1-phenylethanol (**1a**)[82] was chosen as the model substrate to react with cinnamaldehyde **2a**. For ease of NMR and chiral HPLC analysis, the hemiacetal product **3a** was directly converted into **4a** by subsequent dehydroxylation. To our delight, only a single diastereomer was detected for the ^{1}H NMR analysis of the crude product of **4** when diphenylprolinol silyl ether **A** was used as catalyst. To determine the stereochemical outcome of this sequential reaction, NMR HSQC analysis of **4a** was performed to determine the exact locations of all the three continuous chiral hydrogen atoms. Moreover, an NOE experiment of **4a** showed that all three continuous stereocenters were in a *cis*-relationship, which was consistent with our previous observation.[80,81] This assignment in the stereochemistry was further conformed by X-ray crystallographic analysis of **4h**, and its absolute configuration was determined to be (2*S*,3*S*,4*R*).[89] Therefore, the chirality of *S*-β-nitro alcohol had remained during the tandem procedure. In addition, the diastereoselectivity was greatly improved relative to the previous experimental results,[79,80] which indicates the matching role of the adjacent chiral center of β-nitro alcohol.

A series of commonly used chiral secondary amines were then screened as small organic catalysts using benzoic acid as the cocatalyst in chloroform at room temperature. As shown in Table 1, satisfying results were obtained by several different D-diphenylprolinol silyl ethers (**A**−**C**), and the steric hindrance effects of the silyl ethers protection groups were not noticeable (entries 1−3). However, simple unprotected diphenylprolinol **D** provided poor diastereoselectivity albeit with good yield and high enantioselectivity (Table 1, entry 4). D-Proline could also facilitate the process, but the efficiency decreased sharply. Even when the reaction time was extended to 48 h, the transformation did not go to completion (Table 1, entry 5). In contrast, D-prolinamide showed no catalytic activity at all (Table 1, entry 6). In addition, 5 mol % catalyst loading was sufficient for the transformation to go to completion smoothly within 30 h (Table 1, entry 7).

Then a set of organic achiral and chiral acids as well as organic bases were tested as additives as exploratory efforts to improve the efficiency, but none of them could afford better outcomes than benzoic acid. The results are presented in Table 2. In the absence of acid additive, the reaction efficiency declined sharply, while the enantioselectivity was not influenced (Table 2, entry 1). Other substituted benzoic acids delivered similar ee values, in spite of a slower reaction rate (Table 2, entries 3−6). 1-Naphthoic acid and acetic acid could give comparable results (Table 2, entries 7 and 8). Some other chiral acids including L-tartaric acid and protected proline made the process become sluggish (Table 2, entries 9−11). When much stronger camphorsulfonic acid was used, the transformation did not occur at all (Table 2, entry 12). A group of organic bases were then investigated. Among them, only imidazole and 1-Me-imidazole could promote the reaction (Table 2, entries 13−15).

The effect of solvent on this asymmetric cascade process was next investigated. The results are disclosed in Table 3. Alcohols were not good choice because of the slow reaction rate (Table 3, entries 1−3). Halogenated solvents such as chloroform, dichloromethane, and 1,2-dichloroethane (DCE) proved to be the best choices in terms of yield, diastereoselectivity, and enantioselectivity (Table 3, entries 4−6). Acetonitrile and tetrahydrofuran (THF) provided inferior outcomes (Table 3, entries 7 and 8). Toluene provided a good result but needed a rather long reaction time (Table 3, entry 9). Aprotic polar solvent DMF had low efficiency and gave poor diastereoselectivity (Table 3, entry 10). It should be noted that the reaction did not proceed in dioxane (Table 3, entry 11).

On the basis of the above systematic optimization of reaction parameters, the substrate scope of enals was subsequently investigated under the established conditions. The results are listed in Table 4. Generally, a variety of α,β-unsaturated aldehydes could work well with **1a** to give the corresponding products in good yields with excellent enantioselectivities and diastereoselectivities. In most cases, the ^{1}H NMR analysis of the rural product of **4** showed that only a single diastereomer was detected. Chiral HPLC analysis indicated that most of the

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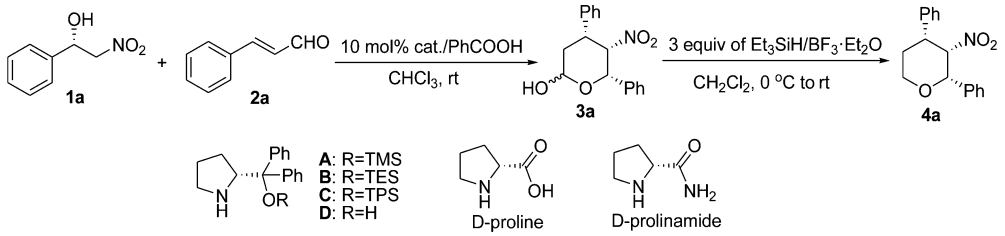
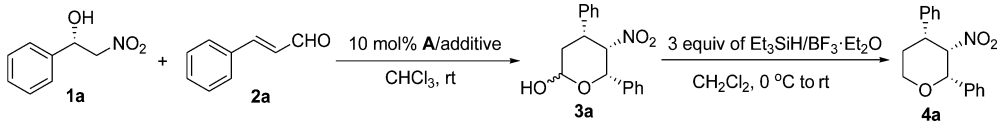
Table 1. Catalyst Screening[a]



entry	catalyst	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**A**	20	96	>19:1	99
2	**B**	24	90	>19:1	99
3	**C**	30	91	>19:1	99
4	**D**	24	82	1:1	99
5	D-proline	48	53	1:1	99
6	D-prolinamide	48	trace	nd[e]	nd[e]
7[f]	**A**	30	95	>19:1	99

[a]Reaction conditions for step 1: 0.2 mmol scale of **1a** with 1.2 equiv of **2a** in the presence of 10 mol % of catalyst and benzoic acid as additive in 1 mL of $CHCl_3$ at room temperature. Reaction conditions for step 2: lactol **3a** (0.2 mmol) dissolved into 2 mL of CH_2Cl_2, 3 equiv of Et_3SiH and BF_3·Et_2O added successively at 0 °C, and the reaction mixture warmed to rt and stirred for several hours. [b]Yield of isolated product **3a**. Yields for step 2 (**4a**) were in the range of 80 to 85%. [c]Determined by ^1H NMR spectroscopy analysis on the crude product of **4a**. [d]The ee value of **4a** was determined by chiral HPLC analysis. [e]Not determined. [f]5 mol % of catalyst **A** and benzoic acid were used.

Table 2. Additive Screening[a]



entry	additive	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	none	35	75	9:1	99
2	benzoic acid	20	96	>19:1	99
3	*p*-nitrobenzoic acid	30	72	9:1	99
4	*p*-iodobenzoic acid	24	93	9:1	99
5	*o*-iodobenzoic acid	24	80	9:1	99
6	salicylic acid	35	77	9:1	99
7	1-naphthoic acid	24	94	>19:1	99
8	acetic acid	24	91	>19:1	99
9	L-tartaric acid	30	65	9:1	99
10	Cbz-L-proline	48	74	>19:1	99
11	Cbz-D-proline	48	85	>19:1	99
12	camphorsulfonic acid	48	trace	nd[e]	nd[e]
13	imidazole	30	81	9:1	99
14	1-Me-imidazole	30	76	9:1	99
15[f]	other organic bases	48	trace	nd[e]	nd[e]

[a]Reaction conditions for step 1: 0.2 mmol scale of **1a** with 1.2 equiv of **2a**, in the presence of 10 mol % of catalyst **A** and additive, in 1 mL of $CHCl_3$ at room temperature. Reaction conditions for step 2 were the same as in Table 1. [b]Yield of isolated product **3a**. Yields for step 2 (**4a**) were in the range of 80 to 85%. [c]Determined by ^1H NMR spectroscopy analysis on the crude product of **4a**. [d]The ee value of **4a** was determined by chiral HPLC analysis. [e]Not determined. [f]Other organic bases used here include DMAP, DABCO, TEA DIPEA, DBU, cinchonine, etc.

expected products **4** were obtained in greater than 99% ee. On one hand, the position of substituents had some effect on the outcomes of the catalytic transformation. In particular, *ortho*-substituted enals always gave lower yields compared with other analogues (Table 4, entries 2, 5, and 7). However, regardless of whether *ortho*-, *meta*- or *para*-positions had been filled, all of the variants could be tolerated well and the enantioselectivities and diastereoselectivities were not affected (Table 4, entries 2−9). On the other hand, the electronic nature of the substituents also did not influence the course of the asymmetric catalytic process. For instance, **4k** bearing an electron-donating methoxyl group worked as well as the wide range of electron-withdrawing halogen groups (Table 4, entry 11). Interestingly, heterocyclic substrate containing a furan ring delivered excellent ee value albeit with moderate yield (Table 4, entry 12).

Having achieved the above results, we turned our attention to the reactivity and generality of diverse chiral *β*-nitro alcohols. The data listed in Table 5 showed that this catalytic cascade reaction was a useful and practical protocol for a wide range of nitro alcohols, as all of the tested substrates could react well with cinnamaldehyde **2a** to provide a single diastereomer of desired product **5**. In general, either the substituent locations or their electronic properties exerted an evident influence on the

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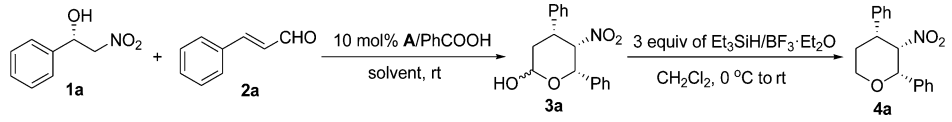
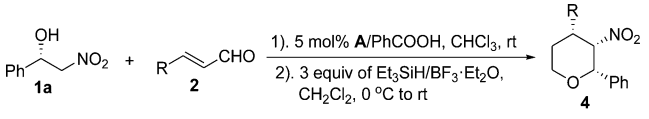
Table 3. Solvent Screening[a]



entry	solvent	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	MeOH	48	72	9:1	99
2	EtOH	30	77	9:1	99
3	*i*PrOH	30	86	9:1	99
4	$CHCl_3$	20	96	>19:1	99
5	CH_2Cl_2	24	93	>19:1	99
6	DCE	24	92	>19:1	99
7	MeCN	40	83	>19:1	99
8	THF	40	65	9:1	99
9	Toluene	35	94	>19:1	99
10	DMF	40	60	3:1	99
11	Dioxane	48	trace	nd[e]	nd[e]

[a]Reaction conditions for step 1: 0.2 mmol scale of **1a** with 1.2 equiv of **2a**, in the presence of 10 mol % of catalyst **A** and benzoic acid, in 1 mL of solvent at room temperature. [b]Yield of isolated product **3a**. Reaction conditions for step 2 were the same as in Table 1. [c]Determined by ^{1}H NMR spectroscopy analysis on the crude product of **4a**. [d]The ee value of **4a** was determined by chiral HPLC analysis. [e]Not determined.

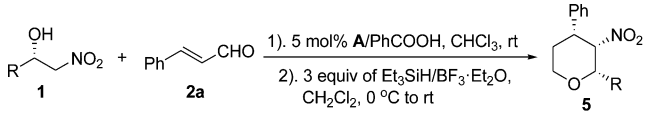
Table 4. Substrate Scope of the Enals[a]



entry	R (product **4**)	yield of step 1[b] (%)	yield of step 2[c] (%)	ee[d] (%)
1	Ph (**4a**)	95	83	99
2	2-MePh (**4b**)	76	82	99
3	3-MePh (**4c**)	88	91	99
4	4-MePh (**4d**)	91	89	99
5	2-ClPh (**4e**)	80	95	99
6	4-ClPh (**4f**)	89	91	99
7	2-BrPh (**4g**)	81	82	98
8	3-BrPh (**4h**)	88	86	99
9	4-BrPh (**4i**)	87	89	99
10	4-FPh (**4j**)	93	88	99
11	4-MeOPh (**4k**)	96	93	99
12	2-furyl (**4l**)	78	71	99

[a]Reaction conditions for step 1: 0.3 mmol of **1a** and 0.36 mmol (1.2 equiv) of **2** were added to a mixture of 5 mol % of catalyst **A** and benzoic acid in 2 mL of $CHCl_3$ at room temperature for 30−48 h. Reaction conditions for step 2: lactol **3** (0.2 mmol) dissolved into 2 mL of CH_2Cl_2, 3 equiv of Et_3SiH and $BF_3{\cdot}Et_2O$ added successively at 0 °C, and the reaction mixture was warmed to rt and stirred for several hours. [b]Yield for step 1 (**3**). [c]Yield for step 2 (**4**). [d]The ee value of **4** was determined by chiral HPLC analysis.

Table 5. Substrate Scope of the Chiral *β*-Nitro Alcohols[a]



entry	R (product **5**)	yield of step 1[b] (%)	yield of step 2[c] (%)	ee[d] (%)
1	2-MePh (**5a**)	91	94	99
2	3-MePh (**5b**)	84	96	99
3	4-MePh (**5c**)	88	91	99
4	2-Cl Ph (**5d**)	90	93	97
5	3-ClPh (**5e**)	94	91	99
6	4-ClPh (**5f**)	89	84	99
7	2-BrPh (**5g**)	90	93	98
8	3-BrPh (**5h**)	87	91	99
9	4-BrPh (**5i**)	91	90	99
10	4-FPh (**5j**)	88	93	99
11	3-NO_2Ph (**5k**)	93	85	99
12	4-NO_2Ph (**5l**)	87	81	98
13	4-CF_3Ph (**5m**)	95	85	99
14	2-thiophenyl (**5n**)	73	81	99
15	PhCHCH (**5o**)	85	79	99
16	$PhCH_2CH_2$ (**5P**)	89	92	99

[a]Identical reaction conditions (see footnote a in Table 4). [b]Yield for step 1 (**3**). [c]Yield for step 2 (**5**). [d]The ee value of **5** was determined by chiral HPLC analysis.

cascade process. For all the substrates employed, extremely high enantioselectivities and diastereoselectivities were afforded while the yields were obtained at a slightly different levels. It is noteworthy that chiral nitro alcohol **1m** derived from *p*-trifluoromethyl benzaldehyde was suitable for this system and gave excellent results (Table 5, entry 13). The trifluoromethyl group was a useful moiety and had been found in a variety of drug and pesticide molecules. Moreover, heterocyclic nitro alcohol **1n** could also work well and delivered the desired product with moderate yield and high ee value (Table 5, entry 14). Furthermore, cinnamaldehyde derivative **1o** can be tolerated, and the double carbon−carbon bonds did not influence the process (Table 5, entry 15). Additionally, aliphatic substrate **1p** was examined, and comparable good results were obtained (Table 5, entry 16).

After finishing the exploration of generality and limitation of the substrate scope, we continued to probe the synthetic utility of this sequential catalytic asymmetric cascade reaction. A successful application to prepare valuable chiral indolizidine alkaloid skeleton **9** is depicted in Scheme 2. In the presence of chiral **L1**/copper complex **I**, 4-oxobutyric acid methyl ester which was easily obtained from commercially available 1,4-butyrolactone could react well with nitromethane to afford optically pure *β*-nitro alcohol **1q** with 98% ee. Then,

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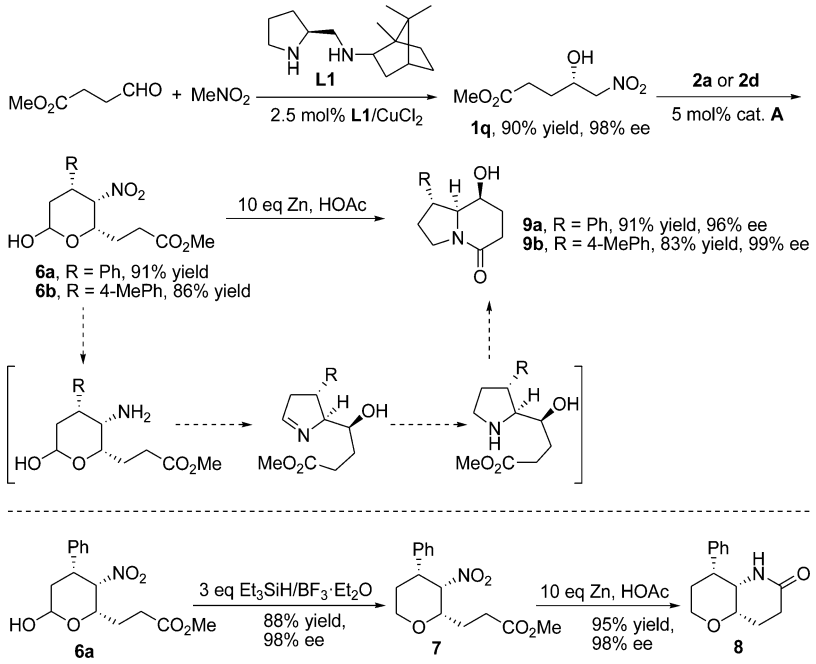
Scheme 2. Synthesis of Indolizidine Alkaloid and Its Relative Heterocycles



diphenylprolinol silyl ether **A** could efficiently promote the Michael addition of **1q** to cinnamaldehyde **2a** and (*E*)-3-*p*-tolylacrylaldehyde **2d**, providing 5-substituted tetrahydropyran lactols **6a** and **6b**. Treatment of **6a** and **6b** with 10 equiv of zinc powder in glacial acetic acid at ambient temperature provided **9a** and **9b**, which means that the reduction of nitro group and successive intramolecular reductive amination and aminolysis would occur. First, the nitro group was readily reduced to the amino motif. Subsequently, the resulting free primary amine attacked the hemiacetal to form imine, which was immediately reduced to secondary amine in situ. Next, intramolecular aminolysis completed the construction of chiral indolizidine alkaloid framework **9** stereoselectively. On the other hand, lactol **6a** could first be dehydroxylated by treatment with 3 equiv of $BF_3{\cdot}Et_2O$ and Et_3SiH in dichloromethane (DCM) to afford **7**. Then, through the same manipulation for **9**, the target fused bicyclic lactam **8** was obtained via the reduction of nitro group and followed by the intramolecular aminolysis reaction. This practical, useful, and simple operation, avoiding costly protecting groups and time-consuming purification procedures for the intermediates, delivered the final expected core structures in high yields without any evident erosion in enantiomeric purities.

CONCLUSION

In conclusion, this work provided an alternative and straightforward stereoselective synthesis of chiral indolizidine alkaloid and its analogues by combining copper-catalyzed asymmetric Henry reaction and organocatalytic Michael addition−hemiacetalization cascade reaction together for the first time. By using low to 2.5 mol % C_1-symmetric chiral diamine−copper complex, the first enantioselective direct Henry reaction was rendered to provide optically pure *β*-nitro alcohols in high yields. Diphenylprolinol silyl ether as an effective chiral secondary amine organocatalyst can promote the second Michael addition cascade reaction between chiral *β*-nitro alcohols and *α*,*β*-unsaturated aldehydes. Through rational design and combination of the above two independent catalytic systems, satisfying results including good yields, excellent enantioselectivities, and diastereoselectivities as well as high functional group compatibility, atom-economy, and step-economy were achieved under mild reaction conditions without any special precautions to exclude air or moisture. Further investigations focusing on the applications of this developed methodology are currently in progress in our laboratory.

EXPERIMENTAL SECTION

General Experimental Methods. THF was dried over Na and distilled prior to use. Nitromethane was dried over anhydrous $CaCl_2$ and distilled prior to use. All the chiral catalysts **L1** and **A**−**D** were prepared according to our previous work or the literature. All of the chiral *β*-nitro alcohols were prepared through asymmetric Henry reaction according to our previous work. Reactions were monitored by TLC analysis using silica gel 60 Å F-254 thin layer plates. Flash column chromatography was performed on silica gel 60 Å, 10−40 *μ*m. Optical rotations were measured by polarimeter in the solvent indicated. ^{1}H NMR spectra were recorded on instruments (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, d = 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, d = 77.0). HRMS was measured on a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer equipped with an EI or ESI source in the positive-ion mode. Enantiomer ratios were determined by chiral HPLC analysis on Chiralcel AD-H, OD-H, IA, and ID-3 in comparison with the authentic racemates. Retention times are given in minutes. The absolute configuration of **4h** was determined to be (2*S*,3*S*,4*R*) by X-ray crystallographic analysis. The same stereochemistry was assumed for assigning the absolute configuration of the rest of the compounds.

Preparation of Racemic Products. All of the racemic nitro alcohols were obtained by the *rac*-Henry reaction, which was catalyzed by 30 mol % of triethylamine with 20 equiv of nitromethane in dichloromethane at room temperature. For the Michael addition cascade reaction, racemic diphenylprolinol silyl ether was used as

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catalyst under the same conditions starting from racemic nitroalcohols.

General Procedure and Characterization of the Products. Step 1. A vial equipped with a stirring bar was charged with chiral β-nitro alcohol **1** (0.3 mmol), benzoic acid (1.8 mg, 0.015 mmol, 5 mol %), and neat chloroform (2.0 mL). After addition of enal **2** (0.36 mmol, 1.2 equiv) and diphenylprolinol trimethylsilyl ether **A** (4.8 mg, 0.015 mmol, 5 mol %), the reaction mixture was stirred at room temperature (about 25 °C) for 30 to 48 h. The reaction was monitored by TLC; when it was complete, the mixture was quenched with aq $NaHCO_3$, extracted with ethyl acetate, dried over anhyd Na_2SO_4, and then concentrated and purified by silica gel column chromatography, eluting with petroleum ether and ethyl acetate to afford the corresponding product **3**.

*(4R,5S,6S)-Tetrahydro-5-nitro-4,6-diphenyl-2H-pyran-2-ol (**3a**):* white solid (Table 1, entry 7, 57 mg, 95% yield); mp 164−166 °C; the ratio of major isomer to minor isomer was 9:1 according to ^{1}H NMR analysis; major isomer: ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ 7.42−7.25 (m, 10H), 6.77 (d, *J* = 3.2 Hz, 1H), 5.70 (s, 1H), 5.66 (d, *J* = 2.4 Hz, 1H), 5.38 (t, *J* = 3.4 Hz, 1H), 3.98 (dt, *J* = 13.6, 4.0 Hz, 1H), 2.85 (t, *J* = 12.2 Hz, 1H), 1.77 (dd, *J* = 13.2, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ 139.4, 137.9, 129.0, 128.6, 128.3, 127.8, 127.6, 126.2, 91.1, 90.3, 68.8, 36.2, 28.4; minor isomer: ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ 7.42−7.25 (m, 10H), 7.14 (d, *J* = 6.4 Hz, 1H), 5.70 (s, 1H), 5.22 (d, *J* = 0.8 Hz, 1H), 5.09(t, *J* = 6.8 Hz, 1H), 3.76 (dt, *J* = 13.6, 4.0 Hz, 1H), 2.60 (t, *J* = 11.2 Hz, 1H), 1.93 (d, *J* = 12.8 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}NO_4Na$ [M + Na]$^+$ 322.1050, found 322.1053; HPLC (Chiralcel AD-H, hexane/2-propanol 70/30, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 22.31 min, $t_{R(minor)}$ = 23.81 min.

Step 2. A vial equipped with a stirring bar was charged with lactol **3** (0.2 mmol) in dry dichloromethane (2.0 mL). To the mixture were added 3 equiv of Et_3SiH and $BF_3{\cdot}Et_2O$ dropwise successively at 0 °C. Then the reaction was allowed to warm to room temperature naturally. The reaction was monitored by TLC; when it was complete, the mixture was quenched with aq $NaHCO_3$, extracted with ethyl acetate, dried over anhyd Na_2SO_4, concentrated, and purified by silica gel column chromatography, eluting with petroleum ether and ethyl acetate to afford the corresponding product **4** or **5**.

*(2S,3S,4R)-Tetrahydro-3-nitro-2,4-diphenyl-2H-pyran (**4a**):* white solid (Table 4, entry 1, 85 mg, 95% yield for step 1; 47 mg, 83% yield for step 2, 99% ee); mp 214−216 °C; $[\alpha]^{23}_D$ = −46.94 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.35−7.24 (m, 10H), 5.06 (t, *J* = 3.4 Hz, 1H), 4.85 (d, *J* = 2.8 Hz, 1H), 4.55 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.82 (td, *J* = 12.0, 2.4 Hz, 1H), 3.43 (dt, *J* = 13.2, 4.4 Hz, 1H), 3.07 (qd, *J* = 13.2, 4.8 Hz, 1H), 1.77 (dt, *J* = 13.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.3, 136.7, 128.9, 128.6, 128.5, 127.9, 127.1, 125.4, 90.1, 79.4, 68.5, 43.8, 23.9; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}NO_3Na$ [M + Na]$^+$ 306.1101, found 306.1108; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 29.58 min, $t_{R(minor)}$ = 25.06 min.

***4a** minor diastereomer:* ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.31−7.27 (m, 6H), 7.22−7.18 (m, 4H), 4.71−4.65 (m, 2H), 4.23−4.20 (m, 1H), 3.81 (td, *J* = 12.0, 2.4 Hz, 1H), 3.56−3.49 (m, 1H), 2.11 (dtd, *J* = 17.2, 12.6, 4.8 Hz, 1H), 2.00−1.96 (m, 1H).

*(2S,3S,4R)-Tetrahydro-3-nitro-2-phenyl-4-o-tolyl-2H-pyran (**4b**):* white solid (Table 4, entry 2, 71 mg, 76% yield for step 1; 49 mg, 82% yield for step 2, 99% ee); mp 167−169 °C; $[\alpha]^{23}_D$ = −141.36 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.38−7.28 (m, 5H), 7.17−7.16 (m, 4H), 4.97 (s, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 4.56 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.86 (td, *J* = 12.0, 2.0 Hz, 1H), 3.64 (dt, *J* = 13.2, 4.0 Hz, 1H), 3.13 (qd, *J* = 13.2, 4.8 Hz, 1H), 2.44 (s, 3H), 1.65 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 136.6, 136.1, 135.1, 130.8, 128.6, 128.4, 127.7, 126.9, 126.4, 125.4, 88.1, 79.3, 68.8, 40.1, 24.2, 19.4; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}NO_3Na$ [M + Na]$^+$ 320.1257, found 320.1262; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 27.27 min, $t_{R(minor)}$ = 14.97 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-2-phenyl-4-m-tolyl-2H-pyran (**4c**):* white solid (Table 4, entry 3, 83 mg, 88% yield for step 1; 54 mg, 91% yield for step 2, 99% ee); mp 152−154 °C; $[\alpha]^{23}_D$ = −49.71 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.34−7.26 (m, 5H), 7.20 (t, *J* = 3.4 Hz, 1H), 7.05 (t, *J* = 9.2 Hz, 3H), 5.05 (t, *J* = 3.2 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 1H), 4.53 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.79 (td, *J* = 12.2, 2.4 Hz, 1H), 3.38 (dt, *J* = 13.2, 4.2 Hz, 1H), 3.04 (qd, *J* = 13.0, 4.8 Hz, 1H), 2.31 (s, 3H), 1.74 (d, *J* = 13.2 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.4, 138.3, 136.7, 128.7, 128.6, 128.5, 128.4, 127.8, 125.3, 124.0, 90.2, 79.3, 68.4, 43.5, 23.8, 21.4; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}NO_3Na$ [M + Na]$^+$ 320.1257, found 320.1261; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 26.57 min, $t_{R(minor)}$ = 20.30 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-2-phenyl-4-p-tolyl-2H-pyran (**4d**):* white solid (Table 4, entry 4, 85 mg, 91% yield for step 1; 53 mg, 89% yield for step 2, 99% ee); mp 195−198 °C; $[\alpha]^{23}_D$ = −59.40 (*c* = 1.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.25−7.19 (m, 5H), 7.04 (s, 4H), 4.95 (t, *J* = 3.4 Hz, 1H), 4.75 (d, *J* = 2.4 Hz, 1H), 4.45 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.71 (td, *J* = 12.0, 2.4 Hz, 1H), 3.30 (dt, *J* = 13.2, 4.4 Hz, 1H), 2.95 (qd, *J* = 13.2, 4.8 Hz, 1H), 2.21 (s, 1H), 1.66 (dd, *J* = 13.6, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 137.5, 136.7, 135.3, 129.6, 128.5, 128.4, 126.9, 125.3, 90.2, 79.3, 68.5, 43.3, 23.9, 21.0; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{19}NO_3Na$ [M + Na]$^+$ 320.1257, found 320.1264; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 26.24 min, $t_{R(minor)}$ = 20.71 min.

*(2S,3S,4R)-4-(2-Chlorophenyl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4e**):* white solid (Table 4, entry 5, 80 mg, 80% yield for step 1; 60 mg, 95% yield for step 2, 99% ee); mp 135−137 °C; $[\alpha]^{23}_D$ = −164.12 (*c* = 1.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.40−7.29 (m, 5H), 7.24−7.19 (m, 4H), 5.23 (t, *J* = 3.2 Hz, 1H), 4.89 (d, *J* = 2.4 Hz, 1H), 4.54 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.93 (dt, *J* = 13.2, 4.2 Hz, 1H), 3.86 (td, *J* = 12.2, 2.4 Hz, 1H), 3.10 (qd, *J* = 13.2, 4.8 Hz, 1H), 1.65 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 136.5, 135.2, 133.5, 129.7, 129.1, 128.5, 128.4, 128.2, 127.6, 125.3, 87.3, 79.1, 68.4, 40.3, 23.6; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}ClNO_3Na$ [M + Na]$^+$ 340.0711, found 340.0717; HPLC (Chiralcel OD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 29.07 min, $t_{R(minor)}$ = 26.96 min.

*(2S,3S,4R)-4-(4-Chlorophenyl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4f**):* white solid (Table 4, entry 6, 89 mg, 89% yield for step 1; 58 mg, 91% yield for step 2, 99% ee); mp 248−250 °C; $[\alpha]^{23}_D$ = −56.70 (*c* = 0.7 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.34−7.26 (m, 7H), 7.20−7.18 (m, 2H), 5.03 (t, *J* = 3.2 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 4.56 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.82 (td, *J* = 12.2, 2.4 Hz, 1H), 3.42 (dt, *J* = 13.2, 4.2 Hz, 1H), 3.03 (qd, *J* = 13.0, 4.8 Hz, 1H), 1.77 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 136.8, 136.4, 133.9, 129.2, 128.6, 128.6, 128.5, 125.3, 89.9, 79.4, 68.4, 43.2, 23.9; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}ClNO_3Na$ [M + Na]$^+$ 340.0711, found 340.0719; HPLC (Chiralcel AD-H, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 27.36 min, $t_{R(minor)}$ = 19.85 min.

*(2S,3S,4R)-4-(2-Bromophenyl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4g**):* white solid (Table 4, entry 7, 92 mg, 81% yield for step 1; 59 mg, 82% yield for step 2, 98% ee); mp 134−137 °C; $[\alpha]^{23}_D$ = −162.83 (*c* = 1.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.58 (dd, *J* = 8.0, 0.8, 1H), 7.37−7.21 (m, 7H), 7.16−7.11 (m, 1H), 5.25 (t, *J* = 3.2 Hz, 1H), 4.89 (d, *J* = 2.8 Hz, 1H), 4.55 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.93−3.83 (m, 2H), 3.10 (qd, *J* = 13.2, 4.8 Hz, 1H), 1.67 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 136.7, 136.5, 133.1, 129.5, 128.9, 128.5, 128.4, 128.3, 128.2, 125.9, 125.3, 124.4, 87.4, 79.2, 68.4, 42.9, 23.8; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}BrNO_3Na$ [M + Na]$^+$ 384.0206, found 384.0209; HPLC (Chiralcel OD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 29.91 min, $t_{R(minor)}$ = 26.49 min.

*(2S,3S,4R)-4-(3-Bromophenyl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4h**):* white solid (Table 4, entry 8, 100 mg, 88% yield for step 1; 62 mg, 86% yield for step 2, 99% ee); mp 172−174 °C; $[\alpha]^{23}_D$ = −61.39 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C,

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TMS) δ 7.40−7.28 (m, 7H), 7.21−7.18 (m, 2H), 5.04 (t, J = 3.4 Hz, 1H), 4.84 (d, J = 2.4 Hz, 1H), 4.54 (dd, J = 11.8, 4.6 Hz, 1H), 3.80 (td, J = 12.0, 2.2 Hz, 1H), 3.39 (dt, J = 13.2, 4.2 Hz, 1H), 3.03 (qd, J = 13.0, 4.8 Hz, 1H), 1.76 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 140.6, 136.4, 131.0, 130. 5, 128.6, 128.5, 125.9, 125.6, 125.3, 122.9, 89.7, 79.3, 68.2, 43.2, 23.7; HRMS (ESI) m/z calcd for $C_{17}H_{16}BrNO_3Na$ $[M + Na]^+$ 384.0206, found: 384.0208; HPLC (Chiralcel AD-H, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 22.64 min, $t_{R(minor)}$ = 19.72 min.

*(2S,3S,4R)-4-(4-Bromophenyl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4i**):* white solid (Table 4, entry 9, 98 mg, 87% yield for step 1; 64 mg, 89% yield for step 2, 99% ee); mp 230−232 °C; $[\alpha]^{23}_D$ = −49.66 (c = 0.8 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.46 (d, J = 8.4 Hz, 2H), 7.34−7.31 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 5.03 (t, J = 3.4 Hz, 1H), 4.86 (d, J = 2.8 Hz, 1H), 4.56 (dd, J = 11.6, 4.0 Hz, 1H), 3.82 (td, J = 12.0, 2.0 Hz, 1H), 3.40 (dt, J = 13.2, 4.0 Hz, 1H), 3.03 (qd, J = 13.2, 4.8 Hz, 1H), 1.77 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 137.3, 136.4, 132.1, 128.8, 128.6, 128.6, 125.3, 122.0, 89.8, 79.4, 68.3, 43.2, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}BrNO_3Na$ $[M + Na]^+$ 384.0206, found 384.0214; HPLC (Chiralcel AD-H, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 28.92 min, $t_{R(minor)}$ = 21.38 min.

*(2S,3S,4R)-4-(4-Fluorophenyl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4j**):* white solid (Table 4, entry 10, 88 mg, 93% yield for step 1; 53 mg, 88% yield for step 2, 99% ee); mp 238−240 °C; $[\alpha]^{23}_D$ = −54.58 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.35−7.29 (m, 5H), 7.23 (dd, J = 8.6, 5.4 Hz, 1H), 7.02 (t, J = 8.6 Hz, 1H), 5.02 (t, J = 3.4 Hz, 1H), 4.86 (d, J = 2.8 Hz, 1H), 4.56 (dd, J = 11.8, 3.8 Hz, 1H), 3.82 (td, J = 12.0, 2.4 Hz, 1H), 3.42 (dt, J = 13.2, 4.4 Hz, 1H), 3.03 (qd, J = 13.2, 4.8 Hz, 1H), 1.77 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 136.5, 134.1, 134.1, 128.8, 128.7, 128.6, 128.5, 125.3, 116.0, 115.8, 90.1, 79.4, 68.4, 43.1, 24.1; HRMS (ESI) m/z calcd for $C_{17}H_{16}FNO_3Na$ $[M + Na]^+$ 324.1006, found 324.1016; HPLC (Chiralcel AD-H, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 24.32 min, $t_{R(minor)}$ = 18.27 min.

*(2S,3S,4R)-Tetrahydro-4-(4-methoxyphenyl)-3-nitro-2-phenyl-2H-pyran (**4k**):* white solid (Table 4, entry 11, 95 mg, 96% yield for step 1; 58 mg, 93% yield for step 2, 99% ee). mp 155−158 °C; $[\alpha]^{23}_D$ = −39.06 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.32−7.22 (m, 5H), 7.15 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.4 Hz, 1H), 5.01 (t, J = 3.4 Hz, 1H), 4.81 (d, J = 2.8 Hz, 1H), 4.51 (dd, J = 11.6, 4.0 Hz, 1H), 3.81−3.76 (m, 1H), 3.73 (s, 3H), 3.36 (dt, J = 12.8, 4.2 Hz, 1H), 3.00 (qd, J = 13.2, 4.8 Hz, 1H), 1.72 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 136.5, 134.1, 134.1, 128.8, 128.7, 128.6, 128.5, 125.3, 116.0, 115.8, 90.1, 79.4, 68.4, 43.1, 24.1; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_4Na$ $[M + Na]^+$ 336.1206, found 336.1215; HPLC (Chiralcel AD-H, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 28.49 min, $t_{R(minor)}$ = 23.74 min.

*(2S,3S,4S)-4-(Furan-2-yl)tetrahydro-3-nitro-2-phenyl-2H-pyran (**4l**):* white solid (Table 4, entry 12, 68 mg, 78% yield for step 1; 39 mg, 71% yield for step 2, 99% ee); mp 133−136 °C; $[\alpha]^{23}_D$ = −3.95 (c = 0.7 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.34−7.29 (m, 6H), 6.29 (dd, J = 3.2, 2.0 Hz, 1H), 6.15 (d, J = 3.2 Hz, 1H), 5.23 (t, J = 3.2 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 4.50 (dd, J = 12.2, 4.2 Hz, 1H), 3.81 (td, J = 12.6, 2.8 Hz, 1H), 3.55 (dt, J = 12.0, 4.0 Hz, 1H), 2.86 (qd, J = 13.2, 4.8 Hz, 1H), 1.89 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 152.2, 142.2, 136.4, 128.6, 128.5, 125.3, 110.5, 106.5, 87.1, 78.8, 68.1, 37.9, 23.2; HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_4Na$ $[M + Na]^+$ 296.0893, found 296.0901; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 30.64 min, $t_{R(minor)}$ = 22.68 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-4-phenyl-2-o-tolyl-2H-pyran (**5a**):* white solid (Table 5, entry 1, 85 mg, 91% yield for step 1; 56 mg, 94% yield for step 2, 99% ee); mp 177−179 °C; $[\alpha]^{23}_D$ = −7.20 (c = 0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.42−7.39 (m, 1H), 7.31−7.22 (m, 5H), 7.15−7.11 (m, 3H), 4.99−4.97 (m, 2H), 4.49 (dd, J = 11.4, 4.6 Hz, 1H), 3.77 (td, J = 12.0, 1.6 Hz, 1H), 3.36 (dt, J = 12.8, 4.0 Hz, 1H), 3.09 (qd, J = 12.8, 4.8 Hz, 1H), 2.31 (s, 3H), 1.72 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.4, 134.8, 133.1, 130.1, 128.8, 128.1, 127.7, 127.0, 126.5, 125.5, 87.9, 76.5, 68.5, 43.4, 23.9, 19.0; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_3Na$ $[M + Na]^+$ 320.1257, found 320.1260; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm): $t_{R(major)}$ = 20.87 min, $t_{R(minor)}$ = 18.28 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-4-phenyl-2-m-tolyl-2H-pyran (**5b**):* white solid (Table 5, entry 2, 79 mg, 84% yield for step 1; 57 mg, 96% yield for step 2, 99% ee); mp 130−133 °C; $[\alpha]^{23}_D$ = −59.84 (c = 1.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.31−7.05 (m, 9H), 5.03 (s, 1H), 4.78 (s, 1H), 4.50 (dd, J = 11.6, 4.8 Hz, 1H), 3.76 (t, J = 12.0 Hz, 1H), 3.38 (dt, J = 13.2, 4.0 Hz, 1H), 3.02 (qd, J = 13.2, 4.8 Hz, 1H), 2.29 (s, 3H), 1.72 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.4, 138.1, 136.5, 129.1, 128.8, 128.3, 127.8, 127.0, 125.9, 122.3, 90.1, 79.2, 68.3, 43.5, 23.8, 21.3; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_3Na$ $[M + Na]^+$ 320.1257, found 320.1253; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 26.85 min, $t_{R(minor)}$ = 19.67 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-4-phenyl-2-p-tolyl-2H-pyran (**5c**):* white solid (Table 5, entry 3, 83 mg, 88% yield for step 1; 54 mg, 91% yield for step 2, 99% ee); mp 187−189 °C; $[\alpha]^{23}_D$ = −36.42 (c = 0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.35−7.22 (m, 7H), 7.15−7.13 (m, 2H), 5.04 (t, J = 3.6 Hz, 1H), 4.84 (d, J = 2.4 Hz, 1H), 4.55 (dd, J = 11.4, 3.8 Hz, 1H), 3.82 (td, J = 12.0, 2.4 Hz, 1H), 3.42 (dt, J = 13.2, 4.0 Hz, 1H), 3.07 (qd, J = 13.4, 5.2 Hz, 1H), 2.31 (s, 3H), 1.78 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.4, 133.6, 129.3, 128.9, 127.9, 127.1, 125.8, 125.2, 90.2, 79.4, 68.5, 43.8, 23.9, 21.1; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO_3Na$ $[M + Na]^+$ 320.1257, found 320.1263; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 29.17 min, $t_{R(minor)}$ = 22.86 min.

*(2S,3S,4R)-2-(2-Chlorophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5d**):* white solid (Table 5, entry 4, 90 mg, 90% yield for step 1; 59 mg, 93% yield for step 2, 97% ee); mp 180−182 °C; $[\alpha]^{23}_D$ = 34.65 (c = 1.3 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.49 (dd, J = 7.0, 2.2 Hz, 1H), 7.37−7.30 (m, 3H), 7.29−7.22 (m, 5H), 5.32 (t, J = 3.2 Hz, 1H), 5.19 (d, J = 2.4 Hz, 1H), 4.55 (dd, J = 11.4, 4.6 Hz, 1H), 3.87 (td, J = 12.4, 2.4 Hz, 1H), 3.45 (dt, J = 13.2, 4.2 Hz, 1H), 3.12 (qd, J = 13.0, 4.8 Hz, 1H), 1.80 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.3, 134.2, 130.9, 129.6, 129.0, 128.9, 127.8, 127.6, 127.4, 127.1, 87.1, 76.4, 68.6, 43.2, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}ClNO_3Na$ $[M + Na]^+$ 340.0711, found 340.0715; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 17.15 min, $t_{R(minor)}$ = 15.74 min.

*(2S,3S,4R)-2-(3-Chlorophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5e**):* white solid (Table 5, entry 5, 94 mg, 94% yield for step 1; 58 mg, 91% yield for step 2, 99% ee); mp 165−167 °C; $[\alpha]^{23}_D$ = −62.03 (c = 1.3 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.36−7.20 (m, 9H), 5.03 (t, J = 3.4 Hz, 1H), 4.77 (d, J = 2.4 Hz, 1H), 4.50 (dd, J = 11.6, 4.0 Hz, 1H), 3.75 (td, J = 12.0, 2.2 Hz, 1H), 3.38 (dt, J = 13.2, 4.2 Hz, 1H), 3.00 (qd, J = 13.2, 4.8 Hz, 1H), 1.73 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.7, 138.1, 134.4, 129.7, 128.9, 128.5, 127.9, 127.0, 125.7, 123.5, 89.8, 78.3, 68.3, 43.4, 23.6; HRMS (ESI) m/z calcd for $C_{17}H_{16}ClNO_3Na$ $[M + Na]^+$ 340.0711, found 340.0705; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 31.30 min, $t_{R(minor)}$ = 25.82 min.

*(2S,3S,4R)-2-(4-Chlorophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5f**):* white solid (Table 5, entry 6, 89 mg, 89% yield for step 1; 53 mg, 84% yield for step 2, 99% ee); mp 216−217 °C; $[\alpha]^{23}_D$ = −49.85 (c = 1.3 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.34−7.29 (m, 6H), 7.25−7.24 (m, 3H), 5.03 (t, J = 3.2 Hz, 1H), 4.84 (d, J = 2.4 Hz, 1H), 4.55 (dd, J = 11.6, 4.0 Hz, 1H), 3.82 (td, J = 12.0, 2.4 Hz, 1H), 3.42 (dt, J = 13.2, 4.4 Hz, 1H), 3.05 (qd, J = 13.2, 5.2 Hz, 1H), 1.78 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.1, 135.2, 134.3, 129.0, 128.8, 128.0, 127.1, 126.8, 89.9, 78.6, 68.5, 43.7, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}ClNO_3Na$ $[M + Na]^+$ 340.0711, found 340.0720; HPLC

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(Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 40.78 min, $t_{R(minor)}$ = 30.80 min.

*(2S,3S,4R)-2-(2-Bromophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5g**):* white solid (Table 5, entry 7, 102 mg, 90% yield for step 1; 67 mg, 93% yield for step 2, 99% ee); mp 188−190 °C; $[\alpha]^{23}_D$ = 60.67 (c = 1.2 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.50 (dd, J = 22.0, 7.8 Hz, 2H), 7.35−7.22 (m, 5H), 7.16 (t, J = 7.6 Hz, 1H), 5.36 (t, J = 3.0 Hz, 1H), 5.14 (d, J = 2.0 Hz, 1H), 4.54 (dd, J = 11.6, 4.8 Hz, 1H), 3.86 (td, J = 12.0, 2.0 Hz, 1H), 3.44 (dt, J = 13.2, 4.0 Hz, 1H), 3.12 (qd, J = 13.2, 4.8 Hz, 1H), 1.79 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.3, 135.7, 132.3, 129.9, 128.9, 128.0, 127.9, 127.8, 127.1, 120.9, 87.0, 78.6, 68.6, 43.2, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}BrNO_3Na$ $[M + Na]^+$ 384.0206, found 384.0214; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 17.32 min, $t_{R(minor)}$ = 14.87 min.

*(2S,3S,4R)-2-(3-Bromophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5h**):* white solid (Table 5, entry 8, 98 mg, 87% yield for step 1; 66 mg, 91% yield for step 2, 99% ee); mp 168−170 °C; $[\alpha]^{23}_D$ = −49.47 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.52 (s, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.35−7.15 (m, 7H), 5.05 (t, J = 3.2 Hz, 1H), 4.81 (d, J = 2.0 Hz, 1H), 4.54 (dd, J = 11.8, 3.8 Hz, 1H), 3.80 (td, J = 12.0, 2.4 Hz, 1H), 3.41 (dt, J = 13.2, 4.2 Hz, 1H), 3.04 (qd, J = 13.2, 4.8 Hz, 1H), 1.77 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.8, 138.1, 131.6, 130.1, 129.0, 128.7, 128.0, 127.1, 124.0, 122.7, 89.7, 78.4, 68.5, 43.7, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}BrNO_3Na$ $[M + Na]^+$ 384.0206, found 384.0211; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 35.73 min, $t_{R(minor)}$ = 26.99 min.

*(2S,3S,4R)-2-(4-Bromophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5i**):* white solid (Table 5, entry 9, 103 mg, 91% yield for step 1; 65 mg, 90% yield for step 2, 99% ee); mp 223−224 °C; $[\alpha]^{23}_D$ = −42.94 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.46 (d, J = 8.4 Hz, 2H), 7.35−7.32 (m, 2H), 7.28−7.22 (m, 5H), 5.03 (t, J = 3.4 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 4.55 (dd, J = 11.6, 3.6 Hz, 1H), 3.82 (td, J = 12.2, 2.4 Hz, 1H), 3.42 (dt, J = 13.2, 4.2 Hz, 1H), 3.05 (qd, J = 13.2, 4.8 Hz, 1H), 1.78 (d, J = 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.1, 135.7, 131.7, 129.0, 128.0, 127.1, 127.0, 122.5, 89.8, 78.6, 68.5, 43.6, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}BrNO_3Na$ $[M + Na]^+$ 384.0206, found 384.0200; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 43.36 min, $t_{R(minor)}$ = 33.97 min.

*(2S,3S,4R)-2-(4-Fluorophenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5j**):* white solid (Table 5, entry 10, 84 mg, 88% yield for step 1; 56 mg, 93% yield for step 2, 99% ee); mp 178−180 °C; $[\alpha]^{23}_D$ = −38.29 (c = 0.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.35−7.31 (m, 4H), 7.28−7.23 (m, 3H), 7.05−7.00 (m, 2H), 5.03 (t, J = 3.4 Hz, 1H), 4.85 (d, J = 2.4 Hz, 1H), 4.55 (dd, J = 11.2, 4.2 Hz, 1H), 3.83 (td, J = 12.2, 2.4 Hz, 1H), 3.43 (dt, J = 13.2, 4.2 Hz, 1H), 3.07 (qd, J = 13.2, 4.8 Hz, 1H), 1.79 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.2, 132.5, 132.4, 129.0, 128.0, 127.2, 127.1, 127.0, 115.7, 115.5, 90.1, 78.8, 68.5, 43.7, 23.8; HRMS (ESI) m/z calcd for $C_{17}H_{16}FNO_3Na$ $[M + Na]^+$ 324.1006; found 324.1012; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 43.08 min, $t_{R(minor)}$ = 27.73 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-2-(3-nitrophenyl)-4-phenyl-2H-pyran (**5k**):* white solid (Table 5, entry 11, 96 mg, 93% yield for step 1; 56 mg, 85% yield for step 2, 99% ee); mp 153−155 °C; $[\alpha]^{23}_D$ = −48.89 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.26 (s, 1H), 8.14−8.12 (m, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.34−7.24 (m, 5H), 5.14 (t, J = 3.4 Hz, 1H), 4.96 (d, J = 2.4 Hz, 1H), 4.57 (dd, J = 11.6, 4.0 Hz, 1H), 3.84 (td, J = 12.4, 2.4 Hz, 1H), 3.48 (dt, J = 13.0, 4.4 Hz, 1H), 3.05 (qd, J = 13.2, 4.8 Hz, 1H), 1.81 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 148.2, 138.8, 137.9, 131.5, 129.6, 129.0, 128.0, 127.0, 123.3, 120.8, 89.6, 77.9, 68.4, 43.4, 23.6; HRMS (ESI) m/z calcd for $C_{17}H_{16}N_2O_5Na$ $[M + Na]^+$ 351.0951, found 351.0961; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 21.07 min, $t_{R(minor)}$ = 19.69 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-2-(4-nitrophenyl)-4-phenyl-2H-pyran (**5l**):* white solid (Table 5, entry 12, 90 mg, 87% yield for step 1; 53 mg, 81% yield for step 2, 99% ee); mp 182−184 °C; $[\alpha]^{23}_D$ = −42.88 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 8.20 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.36−7.25 (m, 5H), 5.11 (t, J = 3.4 Hz, 1H), 4.98 (d, J = 2.4 Hz, 1H), 4.59 (dd, J = 11.8, 4.8 Hz, 1H), 3.86 (td, J = 12.2, 2.4 Hz, 1H), 3.48 (dt, J = 13.0, 4.2 Hz, 1H), 3.07 (qd, J = 13.0, 4.8 Hz, 1H), 1.83 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 148.2, 138.8, 137.9, 131.5, 129.6, 129.0, 128.0, 127.0, 123.3, 120.8, 89.6, 77.9, 68.4, 43.4, 23.6; HRMS (ESI) m/z calcd for $C_{17}H_{16}N_2O_5Na$ $[M + Na]^+$ 351.0951, found 351.0954; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 35.91 min, $t_{R(minor)}$ = 21.14 min.

*(2S,3S,4R)-2-(4-(Trifluoromethyl)phenyl)tetrahydro-3-nitro-4-phenyl-2H-pyran (**5m**):* white solid (Table 5, entry 13, 105 mg, 95% yield for step 1; 60 mg, 85% yield for step 2, 99% ee); mp 229−230 °C; $[\alpha]^{23}_D$ = −50.94 (c = 0.8 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.59 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.36−7.23 (m, 5H), 5.09 (t, J = 3.2 Hz, 1H), 4.91 (s, 1H), 4.57 (dd, J = 11.6, 4.4 Hz, 1H), 3.83 (td, J = 12.2, 2.2 Hz, 1H), 3.45 (dt, J = 13.0, 4.2 Hz, 1H), 3.06 (qd, J = 13.0, 4.8 Hz, 1H), 1.80 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 140.5, 138.0, 129.0, 128.1, 127.1, 125.9, 125.57, 125.54, 125.50, 125.46, 89.7, 78.6, 68.5, 43.7, 23.8; HRMS (ESI) m/z calcd for $C_{18}H_{16}F_3NO_3Na$ $[M + Na]^+$ 374.0974, found 374.0982; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 32.32 min, $t_{R(minor)}$ = 26.44 min.

*(2R,3S,4R)-Tetrahydro-3-nitro-4-phenyl-2-(thiophene-2-yl)-2H-pyran (**5n**):* light yellow solid (Table 5, entry 14, 67 mg, 73% yield for step 1; 47 mg, 81% yield for step 2, 99% ee); mp 117−120 °C; $[\alpha]^{23}_D$ = −37.64 (c = 1.5 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.36−7.24 (m, 6H), 7.02 (d, J = 3.2 Hz, 1H), 6.97 (dd, J = 5.0, 3.8 Hz, 1H), 5.11 (s, 2H), 4.54 (dd, J = 11.8, 4.6 Hz, 1H), 3.85 (td, J = 12.4, 2.4 Hz, 1H), 3.43 (d, J = 12.8 Hz, 1H), 3.04 (qd, J = 13.2, 4.8 Hz, 1H), 1.77 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.9, 138.0, 129.0, 128.0, 127.1, 126.8, 125.4, 123.9, 89.8, 76.3, 68.7, 43.5, 23.8; HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_3SNa$ $[M + Na]^+$ 312.0665, found 312.0660; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 40.70 min, $t_{R(minor)}$ = 32.26 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-4-phenyl-2-styryl-2H-pyran (**5o**):* white solid (Table 5, entry 15, 83 mg, 85% yield for step 1; 49 mg, 79% yield for step 2, 99% ee); mp 175−177 °C; $[\alpha]^{23}_D$ = −45.77 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.35−7.23 (m, 10H), 6.79 (d, J = 16.0 Hz, 1H), 6.11 (dd, J = 16.0, 5.4 Hz, 1H), 4.94 (s, 1H), 4.46 (dd, J = 11.6, 4.8 Hz, 1H), 3.74 (t, J = 12.0 Hz, 1H), 3.32 (dt, J = 12.8, 4.0 Hz, 1H), 3.00 (qd, J = 12.8, 4.8 Hz, 1H), 1.73 (d, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 138.3, 135.9, 133.2, 128.9, 128.5, 128.1, 127.9, 127.1, 126.7, 123.3, 88.9, 77.5, 68.1, 43.3, 23.9; HRMS (ESI) m/z calcd for $C_{19}H_{19}NO_3Na$ $[M + Na]^+$ 332.1257, found 332.1261; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 77.27 min, $t_{R(minor)}$ = 42.14 min.

*(2S,3S,4R)-Tetrahydro-3-nitro-2-phenethyl-4-phenyl-2H-pyran (**5p**):* white solid (Table 5, entry 16, 87 mg, 89% yield for step 1; 57 mg, 92% yield for step 2, 99% ee); mp 100−101 °C; $[\alpha]^{23}_D$ = −86.69 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.33−7.18 (m, 10H), 4.76 (s, 1H), 4.39 (dd, J = 11.6, 4.8 Hz, 1H), 3.63−3.57 (m, 2H), 3.18 (dt, J = 13.0, 4.2 Hz, 1H), 2.97 (qd, J = 13.0, 4.8 Hz, 1H), 2.89−2.82 (m, 1H), 2.80−2.72 (m, 1H), 1.90−1.76 (m, 2H), 1.69 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 140.8, 138.4, 128.9, 128.6, 128.5, 127.8, 127.1, 126.1, 88.8, 75.8, 68.1, 43.3, 33.8, 31.4, 24.1; HRMS (ESI) m/z calcd for $C_{19}H_{21}NO_3Na$ $[M + Na]^+$ 334.1414, found 334.1416; HPLC (Chiralcel AD-H, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 24.72 min, $t_{R(minor)}$ = 17.54 min.

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Synthesis of Indolizidine Alkaloid and Characterization of the Derivatives. *(S)-Methyl 4-Hydroxy-5-nitropentanoate (**1q**).* Ligand **L1** (6 mg, 0.025 mmol, 2.5 mol %) and $CuCl_2·2H_2O$ (4.2 mg, 0.025 mmol, 2.5 mol %) were added to a round bottle containing absolute THF (4 mL). The solution was stirred for 1 h at room temperature to give a green solution. To the resulting solution were added successively 4-oxobutyric acid methyl ester (0.116 g 1 mmol), the nitromethane (0.54 mL, 10 mmol, 10 equiv), and DIPEA (0.174 mL, 1 mmol, 1 equiv), and the tube was introduced in a bath at −20 °C without special precautions to exclude moisture or air. Then the reaction was monitored by TLC; when it finished, the mixture was quenched with 2 M aq HCl, extracted with ethyl acetate, dried over anhyd Na_2SO_4, concentrated, and purified by silica gel column chromatography, eluting with petroleum ether and ethyl acetate to afford the corresponding product **1q** as colorless oil (0.159 g, 90% yield, 98% ee): $[\alpha]^{23}_D$ = −8.13 (*c* = 1.0 in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 4.47−4.38 (m, 3H), 3.70 (s, 3H), 3.42 (br s, 1H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.90−1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 173.9, 80.42, 67.7, 51.9, 29.7, 28.4; HPLC (Chiralcel IA, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 30.86 min, $t_{R(minor)}$ = 32.67 min.

Compounds **6a** and **6b** were prepared according to the general procedure, step 1, by using **1q** to react with **2a** and **2d**, respectively.

*Methyl 3-((2S,3S,4R)-tetrahydro-6-hydroxy-3-nitro-4-phenyl-2H-pyran-2-yl)propanoate (**6a**):* white solid (84 mg, 91% yield); mp 110−112 °C; the ratio of major isomer to minor isomer was 87:13 according to ^{1}H NMR analysis; major isomer: ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ 7.34−7.23 (m, 5H), 6.94 (d, *J* = 6.8 Hz, 1H), 5.12 (s, 1H), 4.82 (t, *J* = 7.2 Hz, 1H), 3.93 (s, 1H), 3.53 (dt, *J* = 13.6, 4.0 Hz, 1H), 2.47−2.42 (m, 3H), 1.83−1.73 (m, 2H), 1.67−1.49 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ 173.1, 139.2, 128.9, 127.6, 127.5, 96.4, 87.6, 73.6, 51.7, 41.5, 31.8, 30.1, 27.3; minor isomer: ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) 7.34−7.23 (m, 5H), 6.58 (d, *J* = 3.2 Hz, 1H), 5.43 (s, 1H), 4.92 (t, *J* = 12.0 Hz, 1H), 4.38 (s, 1H), 3.71 (dt, *J* = 14.4, 4.4 Hz, 1H), 2.73 (t, *J* = 14.0 Hz, 1H), 2.47−2.42 (m, 2H), 1.83−1.73 (m, 2H), 1.67−1.49 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}NO_6Na$ $[M + Na]^+$ 332.1105, found 332.1108.

*Methyl 3-((2S,3S,4R)-tetrahydro-6-hydroxy-3-nitro-4-p-tolyl-2H-pyran-2-yl)propanoate (**6b**):* light yellow solid (83 mg, 86% yield); mp 107−109 °C; the ratio of major isomer to minor isomer was 1:1 according to ^{1}H NMR analysis; ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C, TMS) δ 7.18−7.12 (m, 4H), 6.93 (d, *J* = 6.8 Hz, 0.5H), 6.57 (d, *J* = 3.2 Hz, 0.5H), 5.43 (s, 0.5H), 5.10 (t, *J* = 4.6 Hz, 1H), 4.82 (t, *J* = 7.2 Hz, 0.5H), 4.39 (t, *J* = 3.8 Hz, 0.5H), 3.93 (s, 0.5H), 3.67 (dt, *J* = 13.6, 4.0 Hz, 0.5H), 3.60 (s, 3H), 3.48 (dt, *J* = 13.6, 4.0 Hz, 0.5H), 2.71 (t, *J* = 13.4 Hz, 0.5H), 2.48−2.37 (m, 2.5H), 1.80−1.47 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C, TMS) δ 173.2, 136.8, 136.7, 136.5, 136.1, 129.53, 129.51, 127.4, 96.3, 90.5, 88.6, 87.5, 73.3, 66.0, 51.86, 51.83, 40.9, 35.6, 31.6, 29.9, 28.9, 27.2, 27.1, 21.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}NO_6Na$ $[M + Na]^+$ 346.1261, found 346.1267.

*Methyl 3-((2S,3S,4R)-tetrahydro-3-nitro-4-phenyl-2H-pyran-2-yl)-propanoate (**7**):* prepared in 77 mg, 88% yield and 98% ee according to the general procedure, step 2, starting from **6a** (0.3 mmol scale): white solid; mp 68−70 °C; $[\alpha]^{23}_D$ = −167.85 (*c* = 0.6 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.35−7.31 (m, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 2H), 4.85 (t, *J* = 3.0 Hz, 1H), 4.34 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.79 (dt, *J* = 9.6, 3.0 Hz, 1H), 3.69 (s, 3H), 3.61 (td, *J* = 12.0, 3.0 Hz, 1H), 3.24 (dt, *J* = 13.2, 4.4 Hz, 1H), 2.96 (qd, *J* = 13.0, 4.8 Hz, 1H), 2.56−2.49 (m, 2H), 1.96−1.88 (m, 1H), 1.78−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 173.3, 138.3, 128.8, 127.8, 127.1, 88.6, 75.8, 68.1, 51.6, 43.2, 29.5, 27.3, 24.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}NO_5$ $[M + H]^+$ 294.1336, found 294.1341; HPLC (Chiralcel AD-H, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 16.45 min, $t_{R(minor)}$ = 19.02 min.

*(4R,4aS,8aS)-Hexahydro-4-phenyl-2H-pyrano[3,2-b]pyridin-6(7H)-one (**8**).* A vial equipped with a stirring bar was charged with **7** (59 mg, 0.2 mmol) in acetic acid (3.0 mL). To the mixture was added 10 equiv of zinc powder portionwise, and then the mixture was stirred at room temperature (about 25 °C) for 60 h. The reaction was monitored by TLC; when it was complete, the excess zinc powder was removed by filtration. The filtrate was concentrated under reduced pressure to remove the excess acetic acid. The remaining mixture was neutralized by saturated $NaHCO_3$ aqueous solution until pH = 10 and subsequently extracted with CH_2Cl_2 for three times. The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography eluting with petroleum ether and ethyl acetate to afford the corresponding product **8** as white solid (44 mg, 95% yield, 98% ee): mp 116−118 °C; $[\alpha]^{23}_D$ = −109.26 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 5.06 (br s, 1H), 4.19−4.16 (m, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 3.69−3.64 (m, 2H), 3.14 (dt, *J* = 13.2, 3.2 Hz, 1H), 2.60 (ddd, *J* = 18.0, 13.2, 6.8 Hz, 1H), 2.29−2.12 (m, 3H), 1.83 (tdd, *J* = 13.8, 6.4, 1.8 Hz, 1H), 1.63 (dd, *J* = 13.2, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 172.5, 139.2, 129.2, 127.5, 127.2, 70.7, 67.6, 55.1, 43.7, 26.5, 26.4, 23.2; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1332, found 232.1332; HPLC (Chiralcel IA, hexane/2-propanol 80/20, 0.5 mL/min, UV λ = 254 nm) $t_{R(major)}$ = 21.38 min, $t_{R(minor)}$ = 20.32 min.

*(1R,8S,8aS)-Hexahydro-8-hydroxy-1-phenylindolizin-5(1H)-one (**9a**):* prepared in 42 mg, 91% yield and 96% ee according to the above operation for **8** (0.2 mmol scale); white solid; mp 173−174 °C; $[\alpha]^{23}_D$ = 28.48 (*c* = 1.0 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.37−7.25 (m, 5H), 3.94 (d, *J* = 1.6 Hz, 1H), 3.73−3.57 (m, 3H), 3.46−3.36 (m, 2H), 2.60−2.51 (m, 1H), 2.35 (dd, *J* = 18.0, 7.6 Hz, 1H), 2.25 (dt, *J* = 12.2, 6.2 Hz, 1H), 2.11−2.02 (m, 2H), 1.77 (td, *J* = 12.2, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 169.3, 139.1, 128.7, 127.7, 127.2, 68.7, 61.6, 45.2, 44.9, 29.9, 28.2, 26.2; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}NO_2$ $[M + H]^+$ 232.1332, found 232.1329; HPLC (Chiralcel IA, hexane/2-propanol 90/10, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 37.70 min, $t_{R(minor)}$ = 41.99 min.

*(1R,8S,8aS)-Hexahydro-8-hydroxy-1-p-tolylindolizin-5(1H)-one (**9b**):* prepared in 41 mg, 83% yield and 99% ee according to the above operation for **8** (0.2 mmol scale); colorless oil; $[\alpha]^{23}_D$ = 30.21 (*c* = 0.9 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ 7.22−7.13 (m, 4H), 3.95 (s, 1H), 3.70 (dd, *J* = 21.2, 11.2 Hz, 1H), 3.60 (dd, *J* = 19.4, 7.8 Hz, 1H), 3.44 (d, *J* = 10.8 Hz, 1H), 3.36−3.28 (m, 1H), 2.62−2.49 (m, 1H), 2.44−2.37 (m, 1H), 2.35 (s, 3H), 2.29−2.22 (m, 2H), 2.09−2.01 (m, 2H), 1.86−1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ 168.9, 136.9, 136.3, 129.6, 127.5, 68.8, 62.3, 45.3, 44.9, 30.3, 28.6, 26.3, 20.9; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}NO_2Na$ $[M + Na]^+$ 268.1308, found 268.1315; HPLC (Chiralcel ID-3, hexane/2-propanol 70/30, 0.5 mL/min, UV λ = 210 nm) $t_{R(major)}$ = 15.06 min, $t_{R(minor)}$ = 12.49 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data of all new compounds as well as X-ray structural data (CIF), NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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