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Stereoselective Multicomponent Assembly of Enantiopure Oxazolopiperidines and -azepines

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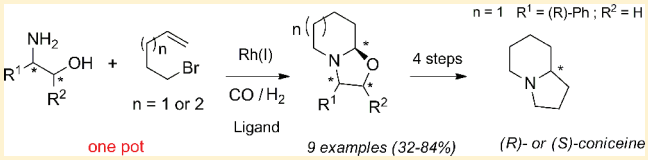
Supporting Information

ABSTRACT: A multicomponent reaction (MCR) based on a cyclohydrocarbonylation (CHC) driven by hydroformylation was set up toward the efficient diastereoselective preparation of oxazolopiperidines (**4a**–**e**) and -azepines (**7a**–**d**). The bicyclic oxazolidines were obtained from chiral *N*-alkenylamino alcohols via transient cyclic iminium intermediates that underwent an intramolecular cyclization from the appendant oxygen. On the basis of a series of different experimental conditions, the diastereocontrol observed during the formation of the oxazolidines is best explained by the stereoelectronic effect induced by an $A^{1,3}$-strain in a common cyclic iminium intermediate (**A**). This new sequence is suitable for diversity oriented syntheses, allowing the preparation of enantiopure (*S*)- and (*R*)-coniceine in five steps from commercially available material.



INTRODUCTION

In the last decades, intense efforts have been dedicated to the design of methods for the construction of functionalized piperidines.[1−3] From all that pertinent chemistry, three templates emerged: (i) the chiral bicyclic lactam **1**, originally introduced by Meyers,[4] further investigated by Amat and Bosch;[5] (ii) the acyl aminal **2** developed by Ojima via a cyclohydrocarbonylation (CHC),[6] recently implemented in our group;[7] and (iii) the cyano-oxazolidine **3a** or the benzotriazole variant **3b** designed, respectively, by Husson and Katritzky (Figure 1).[8,9] Indeed, the versatility of the oxazolidine

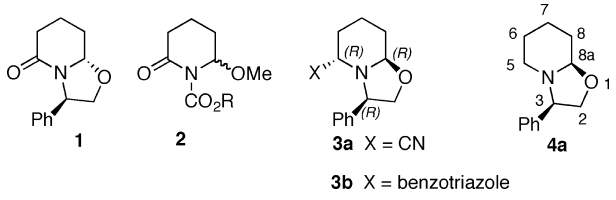


Figure 1. Templates **1**, **2**, **3a**,**b**, and **4a** for the construction of piperidine alkaloids.

chemistry has been demonstrated by several syntheses of natural products and biologically relevant compounds.[10−12]

Recently, our group described an efficient route toward Meyers oxazolidinones **1** through a domino process involving the CHC of the amide constructed from 3-butenoic acid and (*R*)-phenylglycinol.[13] The aldehyde function introduced on the terminal carbon via linear hydroformylation, and the presence of two resident nucleophiles (N and O) produced a transient acyliminium ending into the bicyclic oxazolidinone **1** or analogues that can be implemented as single components into DOS libraries or as key intermediates in the syntheses of piperidine alkaloids.[14]

Indeed, for the rapid construction of complex structures, domino reactions are of great value, but in many cases efforts are needed to reach the key substrates. Conversely, if reaction partners can be taken from the feedstock, the MCR becames an attractive tool for reaching complexity and for the elaboration of sustainable organic syntheses.[15] On the basis of our earlier results, a project was initiated toward the assembly of chiral bicyclic oxazolidines of type **4a** via a multicomponent approach based on the hydroformylation of terminal bromoalkenes (Scheme 1). Bicyclo-oxazolidine **4a** is a stable equivalent of 2-piperideine with the capability of reacting at C2 as an iminium ion or at C3 as an enamine and constitutes a valuable precursor toward substituted piperidines.[16,17] However, the reported preparations of **4a** from **3a** or **3b** have limitations owing the use of a large excess of Ni/Raney for the decyanation step or the removal of benzotriazole at C6.[9,17] In this paper, we describe a new sequence toward oxazolopyridines (**4a**–**e**) or oxazoloazepines (**7a**–**d**) via a CHC–MCR reaction. As an application, short syntheses of (+)- and (−)-coniceine are reported.

RESULTS AND DISCUSSION

As a preliminary study, we examined the viability of the sequence via the intramolecular CHC process[18,19] and investigated the terminal hydroformylation of alkene **6** (Scheme 1a), prepared in 52% yields by microwave-assisted reaction of (*R*)-phenylglycinol **5a** with 4-bromobutene (1 equiv of triethylamine and TBAI).[20] Next, compound **6** was submitted to hydroformylation in THF for 4 h at 65 °C with

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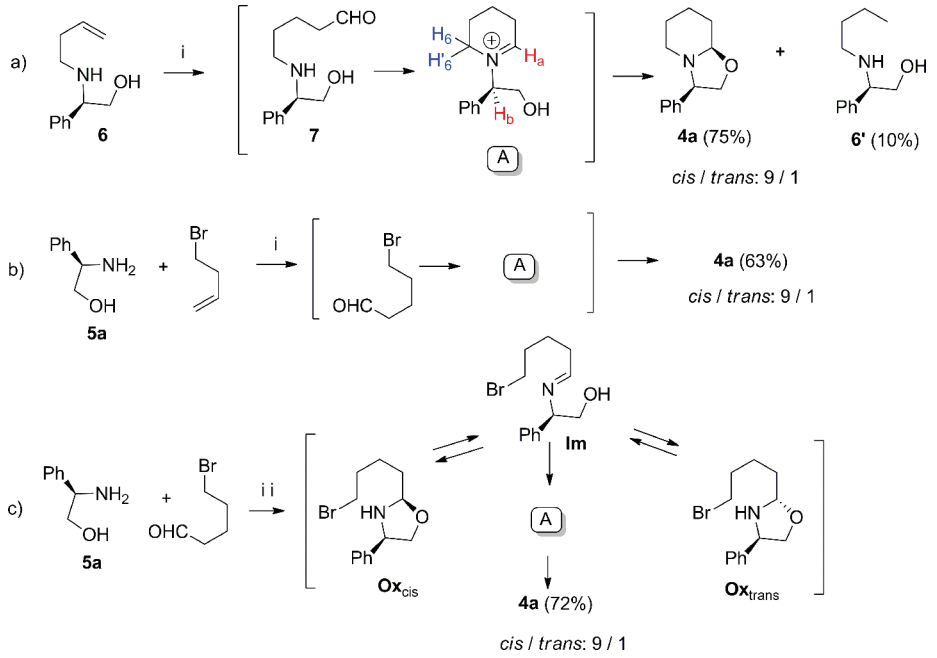
Scheme 1. Three Pathways (a–c) Designed toward Oxazolidine 4a[a]



[a]Reagents and conditions: (i) $Rh(CO)_2acac$ (1% mol), biphephos (2% mol), H_2/CO (1/1) 4 bar THF, 4 h, 65°C; (ii) NEt_3 (1 equiv), THF, rt, 1 day.

the conditions used in our recent work on the synthesis of polysubstituted piperidines:[21] $Rh(CO)_2acac$ as the precatalyst and biphephos as the ligand in a pressurized autoclave with *syngas* (H_2/CO: 1/1, 4 bar). From the reaction mixture, bicyclo-oxazolidine **4a**[16] was isolated as a mixture of epimers at C8a (*cis*/*trans*: 9/1, only distinguishable in NMR, inseparable by chromatography)[22] in 75% yield. Aldehyde **7**, resulting from the linear hydroformylation of alkene **6**, can be considered as the trigger of the domino reaction toward oxazolidine **4a**. In the crude reaction mixture, a minor side product was identified as the *N*-butyl derivative of phenylglycinol **6′**[23] (in 10% yield), resulting from the hydrogenation of the terminal double bound of homoallylamine **6**. Encouraged by these preliminary results, we attempted the MCR–CHC sequence (Scheme 1b). A mixture of 4-bromobutene, (*R*)-phenylglycinol, basic additives, the catalyst, and *syngas* was submitted to the above hydroformylative conditions in an autoclave. As expected, the bicyclic adduct **4a** was isolated in 63% yield. Interestingly, the same epimeric ratio at C8a (*cis*/*trans*: 9/1) was obtained as in the intramolecular version, but no traces of the overreduction adduct **6′** were found in the crude reaction mixture, suggesting that hydroformylation of 4-bromobutene precedes the *N*-alkylation. In order to get a deeper insight into the reaction pathway, a control experiment was designed (Scheme 1c). On the basis of the assumption (see above) that the terminal hydroformylation of 4-bromobutene (to give 5-bromopentanal)[24] is faster than the *N*-alkylation of **5a** with bromobutene, 5-bromopentanal (prepared by oxidation of the corresponding alcohol)[24] was reacted with the amino alcohol **5a** and TEA in THF-d_8 at rt, and the reaction was monitored by ^1H NMR over the time. At first, the signal of the aldehyde disappeared rapidly, and signals corresponding to the oxazolidines and the corresponding imine were identified. After 1 h, a 1:1 mixture of the two oxazolidines ($\mathbf{Ox_{cis}}/\mathbf{Ox_{trans}}$) was observed. In the meantime, the signals corresponding to the imine diminished perceptively: the imine is consumed at the expense of the oxazolidines. After 6 h, both oxazolidines were present, the imine (**Im**) is still visible, and the signals corresponding to bicyclo-oxazolidine **4a** appeared; after 18 h, the signals of compound **4a** were clearly identified as the major compound in the crude mixture, suggesting that the alkylation of the imine (**Im**) is the rate-determining step.

These observations suggested that the imine (**Im**) and two oxazolidines ($\mathbf{Ox_{cis}}$ or $\mathbf{Ox_{trans}}$) are equilibrating under thermodynamic control. Surprisingly none of the oxazolidines $\mathbf{Ox_{cis}}$ or $\mathbf{Ox_{trans}}$ seems to undergo an intramolecular N-alkylation as shown by the absence of NMR signals of the final adduct **4a** in the early stage of the reaction. It seems that $\mathbf{Ox_{cis}}$ or $\mathbf{Ox_{trans}}$ are not the direct precursors of the two epimeric oxazolidines present in **4a**. Therefore, the question about the origin of the distribution of the epimers in **4a** is still open. Epimerization at C8a could be evoked once the bicyclic oxazolidines (**4a**) were formed, but under the presently basic or neutral conditions it is unlikely that ring-opening/closing could occur.[25,26] Such an equilibration has been observed by Husson solely during the epimerization of a crude mixture of **3a** after a treatment with Lewis acids.[27,28] But the fact that in the intramolecular route (a) and both intramolecular CHC routes (b and c) the same ratio of epimers at C8a is observed is intriguing. Therefore, in order to rationalize the above results, the iminium (**A**) is suspected to be the common intermediate in all three pathways a–c. To validate this proposal, our arguments are as follows: (i) For the intramolecular reaction (route a), the hydroformylation delivers the transient terminal aldehyde in **7** and the aminal is formed and evolves toward the cyclic iminium (**A**), which as a strong electrophile is trapped by the resident primary alcohol. The presence of an $A^{1,3}$-strain[29] in iminium (**A**) may be responsible for the formation of the major *cis* epimer at C8a, the thermodynamic compound (Scheme 2). (ii) For the MCR–CHC (route b) or intermolecular (route c) pathways, intermediate **A** can be reached from the imine adduct which is in equilibrium with the two oxazolidines; indeed, the

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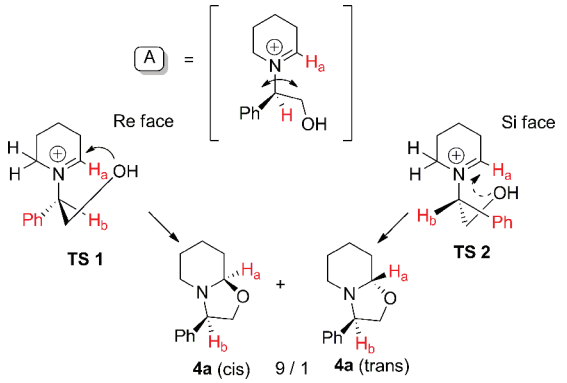
Scheme 2. $A^{1,3}$-Strain in the Iminium Transition States TS1 and TS2



imine nitrogen realizes a substitution on the bromide producing the electrophilic iminium (**A**) which fate has been analyzed before.

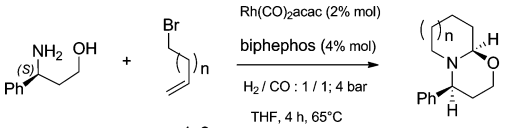
Therefore, it appears that, for stereoelectronic reasons, antiparallel attack and an $A^{1,3}$-strain may constitute the driving forces for the conversion of transient (**A**) to oxazolidine **4a**. The imine hydrogen (H_a) is eclipsing the tertiary hydrogen (H_b) of the chiral auxiliary rather than the phenyl ring; thus, *cis*-**4**, the major isomer is obtained by *Re* face attack on the imine (**TS 1**), whereas for the minor *trans* **4a**, a *Si* face attack is operating (**TS 2**). It is worth mentioning that the cyclization of (**A**) to oxazolidine **4** should be a disfavored process as a 5-*endo*-*trig* ring closure, according to Balwin's rules. But it has been reported that the Baldwin's rules are less tightened for quaternary iminium salts bearing a full charge on the nitrogen.[30]

First to explore the scope of the MCR−CHC, and second to get some support to the transient existence of the intermediate iminium (**A**), the construction of various sizes of decorated oxazolidines was performed from several amino-alcohols **5a**−**e** from the chiral pool and 4-bromobutene or 5-bromopentene as partners in the MCR−CHC reaction. Indeed, the size of the substituent (R^1 and R^2) present on the stereocenter should have an impact on the $A^{1,3}$-strain and consequently modify the *cis*/*trans* ratio of the final oxazolidines. Selecting the standard reaction conditions and the CHC−MCR route (b), the expected bicycles [4.3.0] **4a**−**d**, [5.3.0] **7a**−**d** and the tricyclic oxazolidine **4e** were obtained in good yields but with variable diastereoselectivities (Scheme 3). The observed diasteroselectivity can be correlated with the size of the substituents. In the bicyclic series [4.3.0] for compounds **4a**, **4d**, and **4e** with bulky R^1 and/or R^2 groups (Ph, Me and Ph, and indanyl) a high *cis*/*trans* ratio is observed, whereas with substituents such as R^1 = benz or isPr in **4b** and **4c** the *cis*/*trans* ratio was lower. This observation is counterintuitive as the size of the substituents are roughly similar and suggests to consider also the presence of an $A^{1,2}$-strain in the corresponding iminiums (see Scheme 1, formula **A**). The probable existence of both $A^{1,2}$- and $A^{1,3}$-strain complicates the analysis of the data. A definitive explanation is awaiting further work. In the azepine [5.3.0] series, the corresponding oxazolidines **7a**−**d** were obtained in acceptable yields (except for **7d**), but with an appreciable erosion of the *cis*/*trans* ratio.[31] Probably, accounting for a greater flexibilty in the 7-membered ring, the $A^{1,3}$-strain is operating to a lesser extend.

From all these results, the existence of a transient iminium of type **A** as the common intermediate in the CHC and MCR−CHC sequences has gained some support.

In order to get an additional support for the above mechanistic explanations, we decided to replace (*R*)-phenylglycinol (**5a**) by its homologue (*S*)-3-amino-3-phenylpropanol.[32] In this case, if the MCR−CHC is operating with bromobutene and/or -pentene, a 6-*endo*-*trig* cyclization should take place toward the oxazine, a pathway favored by Baldwin's rules. Indeed, when the MCR−CHC sequence was performed using the standard conditions, the expected *cis*-oxazines **8** and **9** were obtained as *single* diastereomers in 73% and 85% yields, respectively (Scheme 4). The presence of the Bohlman bands

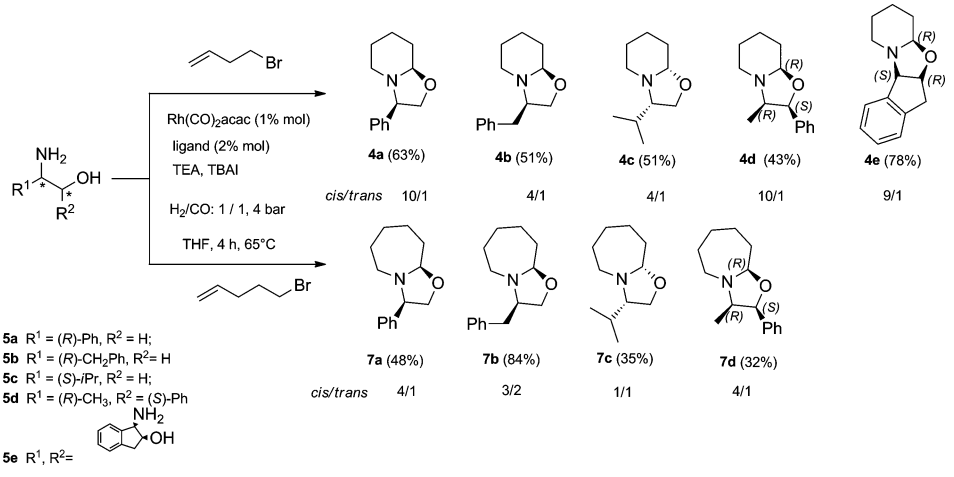
Scheme 4. CHC-MCR Syntheses of Oxazines 8 and 9



8 n = 1 73% de >> 98%
9 n = 2 85% de >> 98%

in IR and extensive NMR studies revealed a *trans*-decalin structure for both oxazines. Despite a greater entropic penalty (one methylene difference) in respect to the formation of **4a** or

Scheme 3. Multicomponent Reactions toward Oxazolidines 4a−e and 7a−d Driven by Hydroformylation



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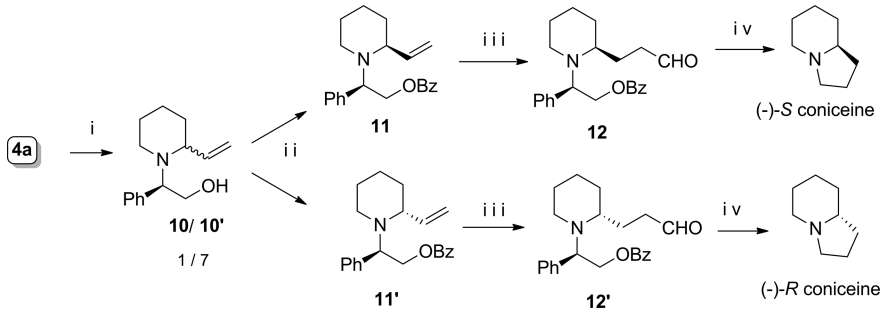
Scheme 5. Synthesis of the Two Epimeric Coniceines[a]



[a]Conditions and reagents: (i) vinylMgBr, THF, 0 °C to rt; (ii) BzCl, TEA, DMAP, THF, rt and separation by column chromatography; (iii) $Rh(CO)_2acac$ (1% mol), biphephos (2% mol), H_2/CO (1/1) 4 bar THF, 4 h, 65°C; (iv) $Pd(OH)_2$ 30% w/w, MeOH, rt, then HCl in Et_2O (2 N).

7a, the $A^{1,3}$-strain in this case seems to operate cleanly as only the *cis* diastereomer is isolated. The above results concur to validate the proposal: that the stereochemical outcome during the formation of the oxazolidines is driven by an efficient $A^{1,3}$-strain.

The significance of oxazolidine **4a** is demonstrated in a short synthesis of the two epimeric (+)- and (−)-coniceines (Scheme 5). Indeed, when **4a** was treated with vinylmagnesium bromide in THF at 0 °C, the vinylpiperidines **10**/**10′** were isolated as an unseparable mixture of diastereomers (1/7 ratio) in 94% yield.[33] The stereochemistry observed for the major isomer **10** is best explained with an axial attack of the vinyl-Grignard to an iminium intermediate as illustrated in several reports.[26,34,35] An improvement of the diastereoselectivity is still imperative, and efforts on this line are underway in our laboratory. Anyway for a convenient chromatographical separation, benzoylation of the primary alcohol was necessary. Each purified diastereomer (**11** or **11′**) was submitted to a terminal hydroformylation under the standard conditions, returning the epimeric aldehydes **12** and **12′**. A final domino hydrogenolysis, encompassing N-deprotection and cyclizing reductive amination gave the natural indolizidine (+)-coniceine and (−)-coniceine in four steps from oxazolidine **4a**. The present synthesis to coniceine compares favorably with recent reported routes in term of number of steps and yields.[36] It is noteworthy that the present synthesis of coniceine is using two times CO and H_2 as the main reagents in the syntheses of **4a**, **10**, and **10′** to achieve two linear hydrofomylations and finally a deprotective hydrogenolysis for reaching coniceine.

CONCLUSION

In conclusion, CHC−MRC driven by hydroformylation of mixtures of chiral amino alcohols and bromo-alkenes generates bicylic oxazolidines in good yields. In these sequences, not only the performance of the hydroformylation has to be considered but even better oxazolidine **4a** and analogues are now easily available in one step on a large scale. Based on a series of experiments comparing intra- or intermolecular routes, the observed diastereoselectivity seems to be correlated with an $A^{1,3}$-strain existing in a transient cyclic iminium. The herein reported access to **4a** should facilitate the assembly of natural products, specially for diversity-oriented syntheses of piperidines or azepines.

EXPERIMENTAL SECTION

General Experimental Methods. All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out in oven-dried or flamed vessels and performed under argon. Solvents were dried and purified by conventional methods prior use. Et_2O and THF were freshly distilled from sodium/benzophenone and dichloromethane was distilled from CaH_2. Toluene was distilled from sodium. **Caution**: the handling of H_2/CO needs special safety equipment. Flash column chromatography was performed with silica gel 60, 0.040−0.063 mm (230−400 mesh). Aluminum-backed plates precoated with silica gel 60 (UV254) were used for thin-layer chromatography and were visualized by staining with $KMnO_4$. ^1H, ^{13}C spectra were recorded on different spectrometers (400 MHz/100 MHz), (300 MHz/75 MHz), or (200 MHz/50 MHz). Conditions are specified for each spectrum (temperature 25 °C unless specified). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; sex, sextuplet; br, broad. Chemical shifts (δ) are given in ppm relative to the resonance of their respective residual solvent peak, $CHCl_3$ (7.27 ppm, ^1H; 77.16 ppm, the middle peak, ^{13}C). The connectivity and relative stereochemistry were deduced from COSY90, HSQC, and HMBC experiments. Infrared spectra were taken with an FT-IR apparatus. High- and low-resolution mass spectroscopy analyses were conducted on the ESI mode. Melting points were determined in open capillary tubes and are uncorrected. Specific rotations were measured using a 10 cm cell with a Na 589 nm filter: values are given in 10^{-1} deg·cm^3·g^{-1}.

(*R*)-2-(But-3-enylamino)-2-phenylethanol (6).[20] A sealed tube containing a solution of (*R*)-phenylglycinol (**5a**) (500 mg, 3.65 mmol) in 15 mL of anhydrous THF, 1 equiv of 4-bromobut-1-ene (371 μL, 3.65 mmol), 1 equiv of triethylamine (507 μL, 3.65 mmol), and 1 equiv of tetrabutylammonium iodide (1.45 g, 3.65 mmol) was stirred at 130 °C for 10 min in a microwave. The solution was quenched with water, extracted by EtOAc, dried on Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH 9/1) to yield the desired product as pale yellow solid (360 mg, 52%): TLC (CH_2Cl_2/MeOH 9/1) R_f 0,33; mp 46−48 °C; $[\alpha]^{20}_D$ −57.4 (*c* 1.5 in $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 3289, 2920, 2838, 1640, 1492, 1453; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39−7.26 (m, 5H), 5.76 (ddt, J = 17.2 Hz, 10.2 Hz, 6.8 Hz, 1H, H_2), 5.11−5.01 (m, 2H, H_1), 3.82 (dd, J = 8.6 Hz, 4.7 Hz, 1H, H_6), 3.73 (dd, J = 10.8 Hz, 4.4 Hz, 1H, H_5), 3.59 (dd, J = 10.6 Hz, 8.7 Hz, 1H, H_6), 2.74 (br s, 2H, NH, OH), 2.71−2.54 (m, 2H, H_4), 2.33−2.22 (m, 2H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 140.4 (C), 136.3 (CH) 128.9 (CH), 127.9 (CH), 127.4 (CH), 116.8 (CH_2), 66.6 (CH_2), 64.7 (CH), 46.4 (CH_2), 34.3 (CH_2); LRMS-ESI *m*/*z* 192.1 $[M + H]^+$.

(3*R*,8a*R*)-3-Phenylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine (*cis*-4a) and (3*R*,8a*S*)-3-Phenylhexahydro-2*H*-oxazolo[3,2-*a*]-pyridine (*trans*-4a). In a reactor under argon containing a solution of 100 mg of **6** (0.52 mmol) in 10 mL of anhydrous THF were added $Rh(CO)_2acac$ (1.4 mg, 1 mol %) and biphephos (8.2 mg, 2 mol %). The solution was stirred for 4 h at 65 °C under a *syngas* pressure of 4 bar (H_2/CO 1/1). The solution was then concentrated and purified by flash chromatography (pentane/EtOAc 9/1) to yield the desired product as brown solid (80 mg, 75%). Mixture of two diastereomers (91/9 *cis*/trans): TLC (pentane/EtOAc 9/1); R_f 0.20; mp 39−41 °C;

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IR (neat) ν_{max}/cm^{-1} 2941, 1453, 1120; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) for *cis* isomer: 7.43−7.23 (m, 5H), 4.17 (dd, J = 7.7 Hz, 7.7 Hz, 1H, H_2), 3.70 (dd, J = 9.7 Hz, 2.9 Hz, 1H, H_3), 3.65 (dd, J = 8.2 Hz, 8.2 Hz, 1H, H_2), 3.54 (dd, J = 8.2 Hz, 8.2 Hz, 1H, H_1), 2.90−2.81 (m, 1H, H_7), 2.08−1.96 (m, 2H, H_4, H_7), 1.93−1.81 (m, 1H, H_5), 1.68−1.46 (m, 3H, H_4, H_6), 1.43−1.25 (m, 1H, H_5), for *trans* isomer (diagnostic peaks only) 4.47−4.38 (m, 2H), 4.29−4.24 (m, 1H), 3.97 (dd, J = 7.9 Hz, 4.4 Hz, 1H), 2.75−2.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer: 139.3 (C), 128.7 (CH), 128.1 (CH), 127.9 (CH), 94.9 (CH), 73.2 (CH_2), 67.4 (CH), 48.1 (CH_2), 30.7 (CH_2), 25.1 (CH_2), 22.8 (CH_2); LRMS-ESI m/z 204.1 $[M + H]^+$.

General Procedure for the *One-Pot* Synthesis. In a reactor under argon containing a solution of the amino alcohol (**5a**−**e**) (100 mg) in 10 mL of anhydrous THF are added 2 equiv of alkyl bromide, 1 equiv of triethylamine, 1 equiv of tetrabutylammonium iodide, 1 mol % of $Rh(CO)_2acac$, and 2 mol % of biphephos. The solution is stirred for 4 h at 65 °C under a *syngas* pressure of 4 bar (H_2/CO 1/1). The solution is then concentrated and purified by flash chromatography to yield the desired product (**4a**−**e** or **7a**−**d**).

(3*R*,8a*R*)-3-Phenylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine (*cis*-4a) and (3*R*,8a*S*)-3-Phenylhexahydro-2*H*-oxazolo[3,2-*a*]-pyridine (*trans* 4a). Reaction between (*R*)-phenylglycinol (**5a**) and 4-bromobut-1-ene without TBAI. Brown solid (63%). Mixture of two diastereomers (91/9 *cis*/*trans*).

(3*R*,8a*R*)-3-Benzylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine (*cis*-4b) and (3*R*,8a*S*)-3-Benzylhexahydro-2*H*-oxazolo[3,2-*a*]-pyridine (*trans*-4b). Reaction between (*R*)-phenylalaninol (**5b**) and 4-bromobut-1-ene without TBAI. Colorless oil (51%). Mixture of two diastereomers (77/23 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.16; IR (neat) ν_{max}/cm^{-1} 2936, 2854, 1496, 1453; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.15 (m, 10H), 4.52 (t, J = 3.4 Hz, 1H, $H_{4'}$), 3.99 (dd, J = 8.0 Hz, 6.8 Hz, 1H, $H_{3'}$), 3.81 (dd, J = 7.7 Hz, 7.7 Hz, 1H, H_3), 3.65 (dd, J = 8.2 Hz, 8.2 Hz, 1H, H_3), 3.56 (dd, J = 9.4 Hz, 2.6 Hz, 1H, H_4), 3.43 (dd, J = 7.8 Hz, 3.7 Hz, 1H, $H_{3'}$), 3.35 (dddd, J = 9.0 Hz, 6.9 Hz, 6.0 Hz, 4.1 Hz, 1H, $H_{2'}$), 3.18−3.13 (m, 1H, H_8), 3.10 (dd, J = 13.5 Hz, 4.3 Hz, 1H, H_1), 3.03 (dd, J = 14.2 Hz, 6.3 Hz, 1H, $H_{1'}$), 2.85 (dddd, J = 9.3 Hz, 8.4 Hz, 7.6 Hz, 4.7 Hz, 1H, H_2), 2.78−2.72 (m, 1H, $H_{8'}$), 2.65 (dd, J = 13.5 Hz, 9.2 Hz, 1H, H_1), 2.60−2.50 (m, 2H, $H_{1'}$, $H_{8'}$), 2.11 (td, J = 10.9 Hz, 3.3 Hz, 1H, H_8), 2.03−1.93 (m, 1H, H_5, $H_{5'}$), 1.93−1.80 (m, 1H, H_6, $H_{5'}$), 1.71−1.23 (m, 4H, H_5, H_6, H_7, $H_{6'}$, $H_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer: 138.7 (C), 128.9 (CH), 128.7 (CH), 126.5 (CH), 94.8 (CH), 70.7 (CH_2), 63.9 (CH), 48.4 (CH_2), 37.9 (CH_2), 30.2 (CH_2), 24.9 (CH_2), 22.5 (CH_2), for *trans* isomer: 139.1 (C), 129.3 (CH), 128.6 (CH), 126.4 (CH), 88.6 (CH), 67.8 (CH_2), 66.4 (CH), 49.5 (CH_2), 39.3 (CH_2), 27.2 (CH_2), 25.1 (CH_2),19.2 (CH_2); HRMS-ESI calcd for $C_{14}H_{20}NO$ 218.1539, found 218.1541.

(3*S*,8a*S*)-3-Isopropylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine (*cis*-4c) and (3*S*,8a*R*)-3-Isopropylhexahydro-2*H*-oxazolo[3,2-*a*]-pyridine (*trans*-4c). Reaction between (*S*)-valinol (**5c**) and 4-bromobut-1-ene without TBAI. Colorless oil (40%). Mixture of two diastereomers (69/31 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.31; IR (neat) ν_{max}/cm^{-1} 2938, 2871, 1456, 1406; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.25 (dd, J = 3.7 Hz, 2.2 Hz, 1H, $H_{4'}$), 4.02 (dd, J = 7.8 Hz, 7.8 Hz, 1H, $H_{3'}$), 3.76 (dd, J = 7.9 Hz, 1H, H_3), 3.67 (dd, J = 7.9 Hz, 2.6 Hz, 1H, H_4), 3.60 (dd, J = 8.1 Hz, 8.1 Hz, 1H, H_3), 3.34 (dd, J = 8.3 Hz, 5.1 Hz, 1H, $H_{3'}$), 2.89 (ddd, J = 10.9 Hz, 4.3 Hz, 4.3 Hz, 1H, H_8), 2.69−2.61 (m, 1H, $H_{8'}$), 2.56−2.38 (m, 3H, H_2, $H_{2'}$, $H_{8'}$), 2.16−2.07 (m, 1H, H_8), 2.03−1.23 (m, 14H, H_1, H_5, H_6, H_7, $H_{1'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$), 0.99 (d, J = 6.6 Hz, 3H, $CH_{3'}$), 0.93 (d, J = 6.8 Hz, 3H, CH_3), 0.86 (d, J = 6.8 Hz, 3H, CH_3), 0.79 (d, J = 6.7 Hz, 3H, $CH_{3'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer 94.4 (CH), 68.1 (CH), 66.5 (CH_2), 47.3 (CH_2), 29.8 (CH_2), 27.7 (CH), 25.1 (CH_2), 22.1 (CH_2), 20.3 (CH_3), 17.1 (CH_3), for *trans* isomer 88.7 (CH), 73.7 (CH), 66.7 (CH_2), 51.2 (CH_2), 31.5 (CH), 26.6 (CH_2), 25.3 (CH_2), 20.9 (CH_3), 19.0 (CH_2), 18.9 (CH_3); HRMS-ESI calcd for $C_{10}H_{20}NO$ 170.1539, found 170.1539.

(2*S*,3*R*,8a*R*)-3-Methyl-2-phenylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine (*cis*-4d) and (2*S*,3*R*,8a*S*)-3-Methyl-2-phenylhexahydro-2*H*-oxazolo[3,2-*a*]pyridine (*trans*-4d). Reaction between (+)-norephedrine (**5d**) and 4-bromobut-1-ene without TBAI. Colorless oil (43%). Mixture of two diastereomers (91/9 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.45; IR (neat) ν_{max}/cm^{-1} 2941, 2855, 1493, 1455; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) for *cis* isomer 7.38−7.21 (m, 5H), 4.97 (d J = 7.9 Hz, 1H, H_3), 3.61 (dd, J = 9.6 Hz, 2.5 Hz, 1H, H_4), 3.07−3.01 (m, 1H, H_8), 2.78 (qd, J = 7.1 Hz, 6.2 Hz, 1H, H_2), 2.13−1.52 (m, 7H, H_5, H_6, H_7, H_8), 0.65 (d, J = 6.5 Hz, 3H, H_1), for *trans* isomer (diagnostic peaks only) 5.39 (d, J = 6.9 Hz, 1H), 4.79 (dd, J = 3.5 Hz, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer 140.4 (C), 128.1 (CH), 127.9 (CH), 127.7 (CH), 94.9 (CH), 82.1 (CH), 61.7 (CH), 48.3 (CH_2), 30.5 (CH_2), 25.1 (CH_2), 22.9 (CH_2), 13.9 (CH_3); HRMS-ESI calcd for $C_{14}H_{20}NO$ 218.1539, found 218.1545.

(4a*S*,5a*S*,10b*R*)-2,3,4,4a,6,10b-Hexahydro-1*H*,5a*H*-indeno-[1′,2′:4,5][1,3]oxazolo[3,2-*a*]pyridine (*cis*-4e). Reaction between (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (**5e**) and 4-bromobut-1-ene without TBAI. Colorless oil (113 mg, 78%). Mixture of two diastereomers (90/10 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.49; IR (neat) ν_{max}/cm^{-1} 2940, 2860, 1491, 1454; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42−7.00 (m, 4 H), 4.93 (t, J = 8 Hz, 1H), 4.61 (d, J = 6 Hz, 1H), 4.06 (s, 1H), 3.11 (2H), 2.96 (m, 1H), 2.63 (m, 1H), 1.80−1.40 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 135.8, (C), 134.3 (C), 126.9 (CH), 126.4 (CH), 126.0 (CH), 124.3 (CH), 91.3 (CH), 82.1 (CH), 72.3 (CH), 42.6 (CH_2), 33.2 (CH_2), 30.6 (CH_2), 25.6 (CH_2), 22.4 (CH_2); HRMS-ESI calcd for $C_{14}H_{18}NO$ 216.1383, found 216.1384.

(3*R*,9a*R*)-3-Phenyloctahydrooxazolo[3,2-*a*]azepine (*cis*-7a) and (3*R*,9a*S*)-3-Phenyloctahydrooxazolo[3,2-*a*]azepine (*trans*-7a).[31] Reaction between (*R*)-phenylglycinol (**5a**) and 5-bromopent-1-ene. Colorless oil (48%). Mixture of two diastereomers (71/29 *cis*/*trans*): TLC (pentane/Et_2O 9/1) R_f 0.44; IR (neat) ν_{max}/cm^{-1} 2926, 2854, 1492, 1451; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.48−7.21 (m, 10H), 4.96 (dd, J = 7.7 Hz, 3.8 Hz, 1H, $H_{3'}$), 4.33−4.25 (m, 2H, H_3, $H_{2'}$), 4.17−4.06 (m, 2H, H_2, $H_{1'}$), 3.76 (dd, J = 9.1 Hz, 6.9 Hz, 1H, H_1), 3.69 (dd, J = 9.0 Hz, 7.1 Hz, 1H, H_2), 3.57 (dd, J = 8.5 Hz, 8.5 Hz, 1H, $H_{2'}$), 2.93−2.79 (m, 2H, H_8, $H_{8'}$), 2.72 (dd, J = 13.1 Hz, 8.1 Hz, 1H, $H_{8'}$), 2.32−2.22 (m, 1H, H_8), 2.15−2.06 (m, 1H, H_4), 1.92−1.43 (m, 15H, H_4, H_5, H_6, H_7, $H_{4'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer 139.8 (C), 128.7 (CH), 127.9 (CH), 127.4 (CH), 97.6 (CH), 73.7 (CH_2), 70.1 (CH), 49.4 (CH_2), 35.5 (CH_2), 28.8 (CH_2), 25.7 (CH_2), 23.7 (CH_2), for *trans* isomer: 141.2 (C), 128.6 (CH), 127.8 (CH), 127.5 (CH), 96.3 (CH), 73.6 (CH_2), 68.7 (CH), 49.5 (CH_2), 32.0 (CH_2), 30.4 (CH_2), 28.6 (CH_2), 23.9 (CH_2); HRMS-ESI calcd for $C_{14}H_{20}NO$ 218.1545, found 218.1543.

(3*R*,9a*R*)-3-Benzyloctahydrooxazolo[3,2-*a*]azepine (*cis*-7b) and (3*R*,9a*S*)-3-Benzyloctahydrooxazolo[3,2-*a*]azepine (*trans*-7b). Reaction between (*R*)-phenylalaninol (**5b**) and 5-bromopent-1-ene. Colorless oil (84%). Mixture of two diastereomers (59/41 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.43; IR (neat) ν_{max}/cm^{-1} 2925, 2853, 1495, 1452; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.16 (m, 10H), 4.73 (dd, J = 8.9 Hz, 3.9 Hz, 1H, $H_{4'}$), 4.11 (dd, J = 9.0 Hz, 3.0 Hz, 1H, H_4), 3.95 (dd, J = 8.2 Hz, 6.6 Hz, 1H, $H_{3'}$), 3.79 (dd, J = 7.9 Hz, 6.9 Hz, 1H, H_3), 3.70 (dd, J = 7.6 Hz, 7.6 Hz, 1H, H_3), 3.43 (dd, J = 8.2 Hz, 7.1 Hz, 1H, $H_{3'}$), 3.26 (dddd, J = 7.9 Hz, 6.7 Hz, 6.7 Hz, 6.7 Hz, 1H, $H_{2'}$), 3.09−2.90 (m, 5H, H_1, H_2, H_9, $H_{1'}$, $H_{9'}$), 2.70−2.54 (m, 3H, H_1, $H_{1'}$, $H_{9'}$), 2.34 (ddd, J = 12.3 Hz, 8.7 Hz, 4.7 Hz, 1H, H_9), 2.06 (dddd, J = 13.0 Hz, 5.3 Hz, 5.3 Hz, 3.0 Hz, 1H, H_5), 2.02−1.94 (m, 1H, $H_{5'}$), 1.83−1.35 (m, 14H, H_5,H_6, H_7, H_8, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer 139.1 (C), 129.2 (CH), 128.5 (CH), 126.4 (CH), 97.9 (CH), 70.9 (CH_2), 66.6 (CH), 50.3 (CH_2), 39.6 (CH_2), 35.0 (CH_2), 28.8 (CH_2), 25.6 (CH_2), 23.5 (CH_2), for *trans* isomer 139.4 (C), 129.3 (CH), 128.5 (CH), 126.3 (CH), 95.1 (CH), 70.3 (CH_2), 67.8 (CH), 51.0 (CH_2), 40.0 (CH_2), 31.4 (CH_2), 30.3 (CH_2), 29.6 (CH_2), 23.2 (CH_2); LRMS-ESI m/z 232.1

(3*S*,9a*S*)-3-Isopropyloctahydrooxazolo[3,2-*a*]azepine (*cis*-7c) and (3*S*,9a*R*)-3-Isopropyloctahydrooxazolo[3,2-*a*]azepine (*trans*-7c). Reaction between (*S*)-valinol (**5c**) and 5-bromopent-1-ene. Colorless oil (35%). Mixture of two diastereomers (50/50 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.77; IR (neat) ν_{max}/cm^{-1} 2925, 2866, 1452, 1383; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.47 (dd, J =

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9.2 Hz, 4.4 Hz, 1H, $H_{4'}$), 4.12 (dd, J = 9.0 Hz, 3.0 Hz, 1H, H_4), 4.0 (dd, J = 8.3 Hz, 7.4 Hz, 1H, $H_{3'}$), 3.79−3.68 (m, 2H, H_3), 3.30 (dd, J = 7.8 Hz, 7.8 Hz, 1H, $H_{3'}$), 3.10 (ddd, J = 13.6 Hz, 10.2 Hz, 1.0 Hz, 1H, $H_{9'}$), 2.94 (ddd, J = 12.2 Hz, 6.1 Hz, 6.1 Hz, 1H, H_9), 2.66−2.54 (m, 2H, H_2, $H_{2'}$), 2.51−2.35 (m, 2H, H_9, $H_{9'}$), 2.05−1.94 (m, 2H, H_5, $H_{5'}$), 1.81−1.32 (m, 16H, H_1, H_5, H_6, H_7, H_8, $H_{1'}$, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$), 0.99 (d, J = 6.7 Hz, 3H, $CH_{3'}$), 0.89 (d, J = 3.2 Hz, 3H, CH_3), 0.87 (d, J = 3.2 Hz, 3H, CH_3), 0.80 (d, J = 6.7 Hz, 3H, $CH_{3'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 97.9 (CH), 95.2 (CH), 73.8 (CH), 70.2 (CH), 68.7 (CH_2), 67.4 (CH_2), 52.9 (CH_2), 50.8 (CH_2), 34.9 (CH_2), 32.6 (CH), 30.8 (CH_2), 30.5 (CH_2), 30.4 (CH), 29.2 (CH_2), 25.7 (CH_2), 24.1 (CH_2), 22.9 (CH_2), 20.5 (CH_3), 19.5 (CH_3), 18.7 (CH_3), 17.4 (CH_3); HRMS-ESI calcd for $C_{11}H_{22}NO$ $[M + H]^+$ 184.1696, found 184.1700.

(2*S*,3*R*,9a*R*)-3-Methyl-2-phenyloctahydrooxazolo[3,2-*a*]azepine (*cis*-7d) and (2*S*,3*R*,9a*S*)-3-Methyl-2-phenyloctahydrooxazolo[3,2-*a*]azepine (*trans*-7d). Reaction between (+)-norephedrine (**5d**) and 5-bromopent-1-ene. Colorless oil (32%). Mixture of two diastereomers (77/23 *cis*/*trans*): TLC (pentane/EtOAc 9/1) R_f 0.63; IR (neat) ν_{max}/cm^{-1} 2928, 2856, 1494, 1454.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.08 (m, 10H), 5.11 (d, J = 5.9 Hz, 1H, $H_{3'}$), 4.96 (dd, J = 9.1 Hz, 3.6 Hz, 1H, $H_{4'}$), 4.89 (d, J = 7.9 Hz, 1H, H_3), 4.04 (dd, J = 8.9 Hz, 2.5 Hz, 1H, H_4), 3.38 (qd, J = 6.6 Hz, 6.6 Hz, 1H, $H_{2'}$), 2.99−2.79 (m, 3H, H_2, H_9, $H_{9'}$), 2.15−1.35 (m, 17H, H_5, H_6, H_7, H_8, H_9, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$), 0.62 (d, J = 6.9 Hz, 3H, $H_{1'}$), 0.59 (d, J = 6.7 Hz, 3H, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) for *cis* isomer 140.6 (C), 128.0 (CH), 126.6 (CH), 97.7 (CH), 82.6 (CH), 63.9 (CH), 49.7 (CH_2), 34.4 (CH_2), 28.1 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 15.3 (CH_3), for *trans* isomer 140.6 (C), 128.2 (CH), 127.6 (CH), 127.2 (CH), 94.9 (CH), 80.7 (CH), 64.6 (CH), 50.2 (CH_2), 33.0 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 23.4 (CH_2), 13.9 (CH_3); HRMS-ESI calcd for $C_{15}H_{22}NO$ 232.1696, found 232.1698.

(4*S*,9a*R*)-4-Phenyloctahydropyrido[2,1-*b*][1,3]oxazine (*cis*-8). Reaction between (*S*)-3-amino-3-phenylpropan-1-ol and 4-bromobut-1-ene without TBAI. Colorless oil (73%): TLC (pentane/EtOAc 9/1) R_f: 0.25; $[\alpha]^{20}_D$ +92.6 (c 1.5 in $CHCl_3$); IR (neat) $\tilde{\nu}_{max}$/cm^{-1} 3026.1, 2940.5, 2844.9, 1491.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.24 (m, 5H), 4.10 (ddd, J = 11.6 Hz, 4.9 Hz, 1.6 Hz, 1H, H_3), 3.70 (ddd, J = 12.6 Hz, 11.1 Hz, 2.4 Hz, 1H, H_3), 3.59 (dd, J = 9.2 Hz, 2.9 Hz, 1H, H_4), 3.17 (dd, J = 11.4 Hz, 3.2 Hz, 1H, H_1), 2.72−2.67 (m, 1H, H_8), 2.13−2.03 (m, 1H, H_2), 1.92−1.86 (m, 1H, H_5), 1.81−1.59 (m, 4H, H_2, H_5, H_7, H_8), 1.49−1.36 (m, 3H, H_7, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 143.5 (C), 128.6 (CH), 127.7 (CH), 127.3 (CH), 93.9 (CH), 68.2 (CH), 67.5 (CH_2), 50.3 (CH_2), 35.6 (CH_2), 32.2 (CH_2), 25.5 (CH_2), 23.7 (CH_2); LRMS-ESI m/z 218.1 $[M + H]^+$.

(4*S*,10a*R*)-4-Phenyloctahydro-2*H*-[1,3]oxazino[3,2-*a*]azepine (*cis*-9). Reaction between (*S*)-3-amino-3-phenylpropan-1-ol and 5-bromobut-1-ene. Colorless oil (85%): TLC (pentane/EtOAc 9/1) R_f 0.31; IR (neat) ν_{max}/cm^{-1} 3024, 2962, 1494; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50−7.19 (m, 5H), 4.33 (d, J = 6.1 Hz, 6.1 Hz, 1H, H_4), 4.21−4.13 (m, 1H, H_3), 3.90−3.75 (m, 2H, H_1, H_3), 2.65 (ddd, J = 14.1 Hz, 9.3 Hz, 1.9 Hz, 1H, H_9), 2.20−1.22 (m, 11H, H_2, H_5, H_6, H_7, H_8, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 143.2 (C), 128.4 (CH), 127.7 (CH), 127.1 (CH), 94.0 (CH), 67.9 (CH_2), 65.7 (CH), 43.4 (CH_2), 36.0 (CH_2), 30.1 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 22.1 (CH_2); LRMS-ESI m/z 232.1 $[M + H]^+$.

(*R*)-2-Phenyl-2-(2-vinylpiperidin-1-yl)ethanol (10/10′)..[32] To a solution of oxazolo-piperidine **4a** (2 g, 9.84 mmol) in 60 mL of THF at 0 °C was added slowly 40 mL of vinylmagnesium bromide (39.35 mmol, 1.0 M in THF). The solution was warmed to room temperature and stirred overnight. The solution was quenched by NH_4Cl, then extracted by EtOAc, dried on Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (pentane/EtOAC 6/4) to yield the desired product as a colorless oil (2.147 g, 94%): TLC (pentane/EtOAc 6/4) R_f 0.43; IR (neat) ν_{max}/cm^{-1} 3396.4, 2930.8, 2853.4, 1642.0; LRMS-ESI m/z 232.1 $[M + H]^+$.

Procedure for 11/11′. To a solution of **10**/**10′** (2.133 g, 9.22 mmol) in 40 mL of CH_2Cl_2 were added 1.18 mL (10.14 mmol) of benzoyl chloride, 1.4 mL of triethylamine (10.14 mmol), and 105 mg (0.92 mmol) of 4-(dimethylamino)pyridine. The mixture was stirred overnight at room temperature. The solution was then hydrolyzed by water, extracted by CH_2Cl_2, dried on Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (pentane/Et_2O 95/5) to yield the desired products **11** and **11′** into two separable diastereomers.

(*R*)-2-Phenyl-2-((*S*)-2-vinylpiperidin-1-yl)ethyl benzoate (11). Colorless oil (309 mg, 10%): TLC (pentane/Et_2O 95/5) R_f 0.31; $[\alpha]^{20}_D$ −66.8 (c 1.5 in $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2931, 1716, 1602, 1449; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.87 (dd, J = 8.3 Hz, 1.5 Hz, 2H), 7.47−7.10 (m, 8H), 5.81 (ddd, J = 17.4 Hz, 10.2 Hz, 8.8 Hz, 1H, $H_{8'}$), 5.15 (dd, J = 17.2 Hz, 1.8 Hz, 1H, $H_{9'}$), 5.12 (dd, J = 10.2 Hz, 1.8 Hz, 1H, $H_{9'}$), 4.78 (dd, J = 9.7 Hz, 6.6 Hz, 1H, $H_{2'}$), 4.48−4.35 (m, 2H, $H_{1'}$, $H_{2'}$), 2.85 (ddd, J = 11.2 Hz, 3.6 Hz, 3.6 Hz, 1H, $H_{3'}$), 2.74 (ddd, J = 9.4 Hz, 3.3 Hz, 3.3 Hz, 1H, $H_{7'}$), 1.73 (ddd, J = 11.2 Hz, 11.2 Hz, 2.6 Hz, 1H, $H_{3'}$) 1.55−0.93 (m, 6H, $H_{4'}$, $H_{5'}$, $H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.6 (C), 142.7 (CH), 136.0 (C), 132.8 (CH), 130.7 (C), 129.7 (CH), 129.0 (CH), 128.4 (CH), 128.0 (CH), 127.4 (CH), 116.2 (CH_2), 64.5 (CH_2), 63.7 (CH), 61.5 (CH), 46.7 (CH_2), 34.6 (CH_2), 26.2 (CH_2), 23.8 (CH_2); HRMS-ESI calcd for $C_{22}H_{26}NO_2$ $[M + H]^+$ 336.1964, found 336.1959.

(*R*)-2-Phenyl-2-((*R*)-2-vinylpiperidin-1-yl)ethyl Benzoate (11′): colorless oil (2.320 g, 75%); TLC (pentane/Et_2O 95/5) R_f 0.47; $[\alpha]^{20}_D$ +43.9 (c 1.5 in $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2931, 1716, 1602, 1449; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, J = 7.7 Hz, 1.5 Hz, 2H), 7.61−7.24 (m, 8H), 5.96 (ddd, J = 17.3 Hz, 10.2 Hz, 8.7 Hz, 1H, H_8), 5.24 (dd, J = 17.3 Hz, 1.6 Hz, 1H, H_9), 5.14 (dd, J = 10.3 Hz, 1.8 Hz, 1H, H_9), 4.86 (dd, J = 11.5 Hz, 5.7 Hz, 1H, H_2), 4.80 (dd, J = 11.2 Hz, 6.6 Hz, 1H, H_2), 4.51 (dd, J = 6.5 Hz, 5.8 Hz, 1H, H_1), 3.43 (ddd, J = 9.0 Hz, 9.0 Hz, 2.8 Hz, 1H, H_7), 2.81 (ddd, J = 11.5 Hz, 4.5 Hz, 3.5 Hz, 1H, H_3), 2.42 (ddd, J = 11.4 Hz, 9.9 Hz, 3.0 Hz, 1H, H_3), 1.81−1.29 (m, 6H, H_4, H_5, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.7 (C), 141.5 (CH), 141.0 (C), 133.0 (CH), 130.4 (C), 129.8 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 126.9 (CH), 116.3 (CH_2), 63.6 (CH), 62.8 (CH_2), 60.6 (CH), 46.2 (CH_2), 34.4 (CH_2), 26.4 (CH_2), 23.9 (CH_2); HRMS-ESI calcd for $C_{22}H_{26}NO_2$ $[M + H]^+$ 336.1964, found 336.1961

(*R*)-2-((*S*)-2-(3-Oxopropyl)piperidin-1-yl)-2-phenylethyl Benzoate (12). In a reactor under argon containing a solution of **11** (137 mg, 0.41 mmol) in 10 mL of anhydrous THF were added $Rh(CO)_2acac$ (1 mg, 1 mol %) and biphephos (6 mg, 2 mol %). The solution was stirred during 4 h at 65 °C under a *syngas* pressure of 4 bar (H_2/CO 1/1). The solution was then concentrated and purified by flash chromatography (pentane/Et_2O 7/3) to yield the desired product as a colorless oil (94 mg, 63%): TLC (pentane/Et_2O 7/3) R_f 0.33; $[\alpha]^{20}_D$ −47.5 (c 1.3 in $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2931, 2855, 2719, 1715; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.66 (t, J = 1.6 Hz, 1H, H_{10}), 7.93−7.77 (m, 2H), 7.51−7.11 (m, 8H), 4.69 (dd, J = 11.1 Hz, 7.0 Hz, 1H, H_2), 4.39 (dd, J = 11.3 Hz, 6.1 Hz, 1H, H_2), 4.25 (dd, J = 7.0 Hz, 6.1 Hz, 1H, H_1), 2.86−2.70 (m, 1H, H_3), 2.62−2.24 (m, 3H, H_7, H_9), 2.20−2.09 (m, 1H, H_3), 1.99−1.83 (m, 2H, H_8), 1.63−1.12 (m, 6H, H_4, H_5, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.7 (CH), 166.5 (C), 138.3 (C), 133.1 (CH), 130.4 (C), 129.7 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 66.1 (CH_2), 61.5 (CH), 55.1 (CH), 45.2 (CH_2), 40.3 (CH_2), 28.9 (CH_2), 24.7 (CH_2), 22.2 (CH_2), 22.0 (CH_2); HRMS-ESI calcd for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2069, found 366.2064.

(*R*)-2-((*R*)-2-(3-Oxopropyl)piperidin-1-yl)-2-phenylethyl Benzoate (12′). In a reactor under argon containing a solution of **11′** (335 mg, 1.00 mmol) in 10 mL of anhydrous THF were added $Rh(CO)_2acac$ (2.6 mg, 1 mol %) and biphephos (16 mg, 2 mol %). The solution was stirred during 4 h at 65 °C under a *syngas* pressure of 4 bar (H_2/CO 1/1). The solution was then concentrated and purified by flash chromatography (pentane/Et_2O 7/3) to yield the desired product as a colorless oil (304 mg, 83%): TLC (pentane/Et_2O 7/3) R_f 0.33; $[\alpha]^{20}_D$ +24.5 (c 1.5 in $CHCl_3$); IR (neat) ν_{max}/cm^{-1} 2931, 2855, 2719, 1715; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.78 (t, J = 1.6 Hz, 1H, H_{10}), 8.03−7.91 (m, 2H), 7.63−7.25 (m, 8H), 4.79 (dd, J = 11.4 Hz, 5.6 Hz, 1H, H_2), (dd, J = 4.59 Hz, 6.3 Hz, 1H, H_2), 4.37 (dd, J =

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6.0 Hz, 6.0 Hz, 1H, H_1), 2.93−2.85 (m, 1H, H_7), 2.80−2.71 (m, 1H, H_3), 2.66−2.57 (m, 1H, H_3), 2.54−2.41 (m, 2H, H_9), 2.19−2.06 (m, 1H, H_8), 1.94−1.82 (m, 1H, H_8), 1.80−1.31 (m, 6H, H_4, H_5, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.6 (CH), 166.6 (C), 141.4 (C), 133.2 (CH), 130.3 (C), 129.8 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.5 (CH), 65.4 (CH_2), 61.1, 55.4, 44.8 (CH_2), 40.6 (CH_2), 28.1 (CH_2), 24.5 (CH_2), 22.0 (CH_2), 21.9 (CH_2); HRMS-ESI calcd for $C_{23}H_{28}NO_3$ $[M + H]^+$ 366.2069, found 366.2060.

(*S*)-(−)-Coniceine, HCl. To a solution of **12** (94 mg, 0.26 mmol) in 5 mL of MeOH was added 30% in weight of $Pd(OH)_2$ (28 mg). The solution was stirred overnight. The solution was filtered. HCl in Et_2O was added to form the corresponding salt, which was then concentrated and purified by flash chromatography (CH_2Cl_2/MeOH 9/1) to yield the desired product as a white solid (32 mg, 77%): TLC (CH_2Cl_2/MeOH 9/1) R_f 0.38; mp 175−176 °C; $[\alpha]^{20}_D$ +1.4 (*c* 1.0 in EtOH); IR (neat) ν_{max}/cm^{-1} 3396, 2945, 1644, 1549; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.34−11.33 (m, 1H, NH), 3.88−3.53 (m, 2H), 2.96−2.54 (m, 3H), 2.44−1.73 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 67.3 (CH), 52.6 (CH_2), 52.2 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 19.7 (CH_2); LRMS-ESI *m*/*z* 126.1 $[M + H]^+$.

(*R*)-(+)-Coniceine, HCl. To a solution of **12′** (232 mg, 0.63 mmol) in 5 mL of MeOH was added 30% in weight of $Pd(OH)_2$ (70 mg). The solution was stirred overnight. The solution was filtered. HCl in Et_2O was added to form the corresponding salt, which was then concentrated and purified by flash chromatography (CH_2Cl_2/MeOH 9/1) to yield the desired product as a white solid (83 mg, 81%): TLC (CH_2Cl_2/MeOH 9/1) R_f 0.38; mp 175−176 °C; $[\alpha]^{20}_D$ −1.5 (*c* 1.0 in EtOH) [lit.[36] $[\alpha]^{23}_D$ −1.5 (*c* 1.0 in EtOH)]; IR (neat) ν_{max}/cm^{-1} 3396.9, 2945.1, 1644.9, 1549.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.34−11.33 (m, 1H, NH), 3.88−3.53 (m, 2H), 2.96−2.54 (m, 3H), 2.44−1.73 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 67.3 (CH), 52.6 (CH_2), 52.2 (CH_2), 28.5 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 22.8 (CH_2), 19.7 (CH_2); LRMS-ESI *m*/*z* 126.1 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

Experimental characterization data; ^{1}H and ^{13}C for all compounds **4a−e**, **7a−d**, **8**, **9**, **10/10′**, **11/11′**, **12/12′**, (+)-coniceine, and (−)-coniceine. 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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■ DEDICATION

This paper is dedicated to Professor Henri-Philippe Husson for his authoritative contribution to heterocyclic chemistry.

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