Synthetic Studies of *cis*-3a-Aryloctahydroindole Derivatives by Copper-Catalyzed Cyclization of *N*-Allyltrichloroacetamides: Facile Construction of Benzylic Quaternary Carbons by Carbon−Carbon Bond-Forming Reactions

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Cyclization of *N*-(2-aryl-2-cyclohexen-1-yl)trichloroacetamides by a copper catalyst was investigated. It is crucially important for successful cyclization under mild conditions that alkoxycarbonyl groups are introduced to the nitrogen atom of the *N*-allyltrichloroacetamides as well as that CuCl(bipyridine) is used as the catalyst. Three compounds, *N*-(2-phenyl-2-cyclohexen-1-yl)-, *N*-[2-(3,4-dimethoxyphenyl)-2-cyclohexen-1-yl]-, and *N*-[2-(3,4-methylenedioxyphenyl)-2-cyclohexen-1-yl]-trichloroacetamides, where the Cbz or MeO_2C- group was attached to the nitrogen atom, were instantly converted to the corresponding trichlorinated *cis*-3a-aryloctahydroindol-2-ones in high yields at room temperature. The reactions offer a facile access to alkaloid skeletons such as mesembrines and crinines; as the simplest examples, total synthesis of (±)-mesembrane and (±)-crinane was accomplished. The effect of alkoxycarbonyl substituents in the amide group was compared with that of the methyl substituent. *N*-Methyl-*N*-(2-phenyl-2-cyclohexen-1-yl)trichloroacetamide quickly reacted in the presence of CuCl(bipyridine) catalyst; however, the products were a mixture of complicated materials including a small amount of the desired lactam. The role of the alkoxycarbonyl group was discussed in terms of rate of rotation of the N−C bond in the *N*-allyltrichloroacetamides; variable-temperature NMR studies and X-ray structure determination of related compounds were carried out as supporting evidence.

Introduction

Transition metal catalyzed addition reaction of polyhalocarbons to alkenes has become an important carbon−carbon bond-forming reaction in organic synthesis.[1,2] The intramolecular version of this reaction provides a convenient method for construction of various ring systems including skeletons of biologically active compounds.[3−5] In particular, cyclization of *N*-allyltrichloroacetamides affording α,α,γ-trichlorinated γ-lactams have found wide applicability to syntheses of the various pyrrolidinone skeletons including precursors of alkaloids.[6−8] The *cis*-3a-aryloctahydroindole nuclei are seen in many naturally occurring alkaloids and continue to be of interest as synthetic targets.[9] This skeleton has aryl groups at the junction of the two fused rings. Construction of these ring systems by carbon−carbon bond-forming reactions at the position shown in Figure 1 has recently received much

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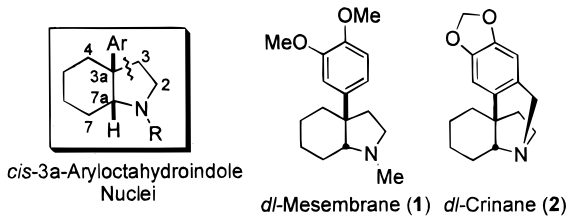
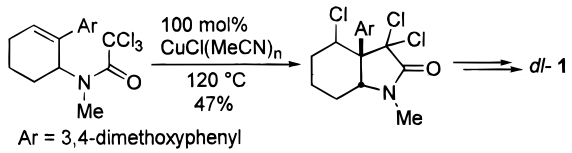


Figure 1.

Scheme 1

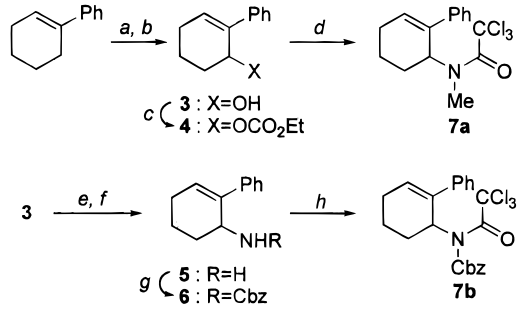


attention in terms of effective construction of quaternary carbons by carbon−carbon bond-forming reactions.

In 1985, we reported that copper-mediated radical cyclization of *N*-methyl-*N*-[2-(3,4-dimethoxyphenyl)cyclohexen-1-yl]trichloroacetamide was one means of solving this problem: the reaction proceeded by the catalysis of CuCl in MeCN at 120−140 °C in a sealed tube. The resulting bicyclic lactam was transformed to (±)-mesembrane, a degradation product of mesembrine alkaloid.[8e] Although the reaction was accomplished successfully, the yield of the product was below 50% even with an increase in the amount of the catalyst to 100%. An analogous reaction was later reported by Ishibashi and Ikeda, who stated that $RuCl_2(PPh_3)_3$-catalyzed cyclization of the *N*-methyl-*N*-(2-arylcyclohexen-1-yl)-α-thiophenyl-α-chloroacetamides at 140 °C;[8a] however, the yield of the product was not satisfactory (~57%) even in the presence of large amounts of the ruthenium catalyst (~20 mol %). In a similar approach, tin-mediated reductive radical cyclizations were devised by Stork et al.[10a] and Ishibashi et al.[10b] Sterically bulky substituents attached to the nitrogen atom of the amide group allow efficient cyclization of *N*-(2-arylcyclohexen-1-yl)haloamide derivatives under milder conditions; however, simple reduction of the halide also occurred as a serious side reaction. In our initial studies on transition metal-catalyzed cyclization of *N*-allyltrichloroacetamides, we found that the reaction generally occurred at above 100 °C. Our efforts to lower the reaction temperature allowed the discovery of highly efficient catalyst systems, a 1:1 mixture of cuprous salts and bidentate diamine ligand such as 2,2′-bipyridine (bipy) or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). Another factor in the cyclization at lower temperature is selection of the substituent on the amide nitrogen; introduction of electron-withdrawing groups such as Ts, Cbz, and *t*-Boc resulted in the cyclization under mild conditions.[6a,d] As a typical example, cyclization of *N*-tosyl-*N*-allyltrichloroacetamide proceeded at room temperature with turnover >80. Use of the CuCl(bipy) catalyst and introduction of Ts group on the nitrogen atom provided successful transformation of α,α-dichlorocarbonyl compounds, which had been difficult to achieve by a conventional method, under mild conditions.[6e]

These new findings prompted us to revisit the problematic cyclization of *N*-(2-phenyl-2-cyclohexen-1-yl)-

Scheme 2[a]



[a] Reagents and conditions: (a) $Hg(OAc)_2$, AcOH, 95 °C, 58%; (b) KOH, aq MeOH, rt, 98%; (c) pyridine, $ClCO_2Et$, Et_2O, rt, 90%; (d) cat. $Pd(OAc)_2$, PPh_3, aq $MeNH_2$, MeCN, 40 °C, then NEt_3, CCl_3COCl, Et_2O, rt, 80%; (e) $(NCO_2Et)_2$, phthalimide, PPh_3, THF, rt, 68%; (f) $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 79%; (g) NEt_3, $ClCO_2Bn$, Et_2O, 0 °C → rt, 87%; (h) *n*-BuLi, CCl_3COCl, THF, −45 °C → rt, 66%.

trichloroacetamides, which might be improved by use of CuCl(bipy) as catalyst and introduction of electron-withdrawing groups on the nitrogen atom. Herein, we report that *N*-alkoxycarbonyl-*N*-(2-aryl-2-cyclohexen-1-yl)trichloroacetamides successfully cyclized to give the corresponding products having *cis*-3a-aryloctahydroindole skeletons under mild conditions, and by means of this reaction, total synthesis of mesembrane and crinane was accomplished. We also observed that attempted cyclization of the *N*-methyl analogue under similar conditions afforded a mixture of intractable products. The effect of the N-substituent was discussed in terms of ease of N−C rotation of the trichloroacetamide; variable-temperature NMR studies as well as structural analyses of related *N*-benzyl- and *N*-tosyl-*N*-allyltrichloroacetamides were also reported as supporting evidence to suggest the importance of the N−C rotation.

Result and Discussion

Effects of N-Substituents in Cyclization of *N*-(2-Phenyl-2-cyclohexen-1-yl)trichloroacetamide Derivatives. Trichloroacetamides **7a** (*N*-Me) and **7b** (*N*-Cbz: carbobenzyloxy) were prepared from commercially available 1-phenylcyclohexene as outlined in Scheme 2. Treatment of 1-phenylcyclohexene with $Hg(OAc)_2$ followed by hydrolysis of the formed acetate afforded an allyl alcohol **3**,[11] which was converted to **4** by reaction with $ClCO_2Et$. Palladium-catalyzed substitution of the $EtOCO_2$ group by MeNH moiety followed by trichloroacetylation of the resulting amine yielded *N*-methyl-*N*-(2-phenyl-2-cyclohexen-1-yl)trichloroacetamide **7a**. The allyl alcohol **3** was subjected to the Mitsunobu reaction to afford an allylic amine **5**,[12] which was transformed to a *N*-Cbz derivative **6**. Trichloroacetylation of **6** yielded **7b** as the *N*-Cbz analogue of **7a**.

The reaction of trichloroacetamide **7a** was carried out in dichloromethane at from room temperature to 40 °C using a 1:1 mixture of CuCl(bipy) as the catalyst. Although all of the starting materials disappeared within 1 h, the desired bicyclic γ-lactam **8a** was available in less than 20% yield, and many intractable byproducts were formed concomitantly (Scheme 3). The yield of **8a** was

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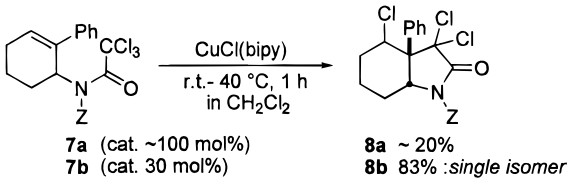
Scheme 3



7a (cat. ~100 mol%) **8a** ~ 20%
7b (cat. 30 mol%) **8b** 83% :*single isomer*

not improved by changing the reaction temperature (−15 to ~40 °C) or by increasing amount of the catalysts from 30 to 100 mol %. On the other hand, cyclization of the *N*-Cbz analogue **7b** proceeded smoothly at room temperature in the presence of 30 mol % of the CuCl(bipy) catalyst to afford the desired γ-lactam **8b** in 83% yield. The ^{1}H NMR spectra of the crude product showed exclusive formation of only one diastereomer of **8b** and no detectable byproducts. The stereochemistry of **8b** was elucidated by X-ray crystallography (Figure 2); the relationship between the angular phenyl group and the proton was cis, whereas that between the phenyl group and the chlorine atom in the six-membered ring was trans. Both the phenyl group and the chlorine atoms occupy the axial position of the cyclohexane ring.[13] Although successful cyclization proceeded with lower concentration of the catalyst, deactivation of the catalyst quickly took place. In fact, the yield of **8b** was 66% with recovery of **7b** (22%), when the reaction was carried out in the presence of 10 mol % of the catalyst.

Successful cyclization of **7b** prompted us to explore a more direct synthetic method for *N*-alkoxycarbonyl-*N*-allyltrichloroacetamides. The allyl cyanate-to-isocyanate rearrangement reported by Ichikawa and Isobe provides a good method to synthesize **10** from **3** via the [3.3]-sigmatropic rearrangement.[14] Reaction of **3** with 2 equiv of trichloroacetylisocyanate was followed by hydrolysis with potassium carbonate in aqueous methanol to give the carbamate **9** (Scheme 4). Treatment of **9** with trifluoromethanesulfonic anhydride (Tf_2O) and diisopropylethylamine at −78 °C followed by addition of lithium methoxide afforded the *N*-allylurethane **10** in 72% yield from **3**. Cyclization of the trichloroacetamide **11** in the presence of 30 mol % of CuCl(bipy) proceeded smoothly to give the desired γ-lactam **12** in 88% yield as a single isomer. To confirm the stereochemistry of angular substituents of **12**, the lactam was subjected to reductive dechlorination with 4 equiv of tributyltinhydride to give **13** in 79% yield. Deprotection of **13** with 5 equiv trimethylsilyliodide (TMSI) in refluxing dichloromethane afforded the known *cis*-3a-phenyloctahydroindol-2-one **14** in good yield.[15]

Synthesis of Mesembrane and Crinane. Success of the above experiments encouraged us to apply the copper-

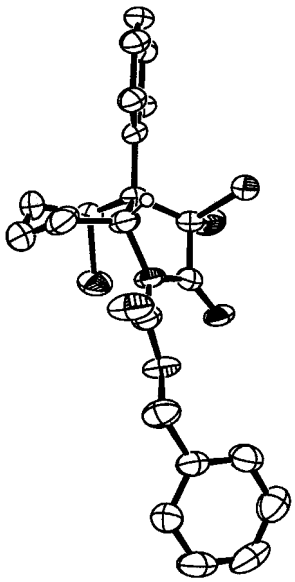
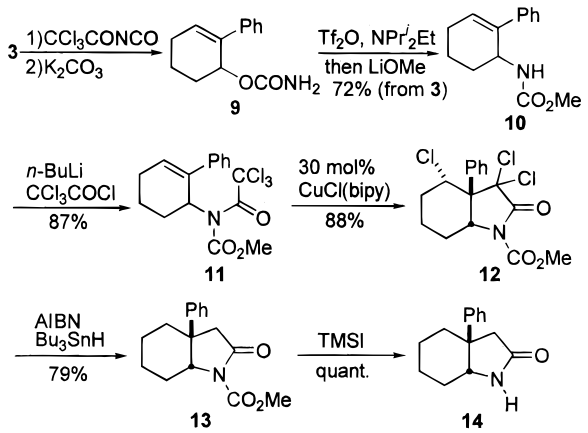


Figure 2. The ORTEP representation of the X-ray crystal structure of lactam **8b**.

Scheme 4



catalyzed cyclization to total syntheses of mesembrane and crinane. According to the literature method,[16] 6-aryl-3-cylohexen-1-ones **16a** and **16b** were prepared by the Diels−Alder reaction of 2-aryl-nitroolefines **15a** and **15b**, respectively, with butadiene followed by the Nef reaction (Scheme 5). The enones **16a** and **16b** were isomerized to **17a** and **17b**, respectively, by catalysis of $RhCl_3$ in ethanol.[17] Reduction of the formed enone with $LiAlH_4$ gave the corresponding allyl alcohol **18a** or **18b** in moderate yield. *N*-Allylurethanes **19a** and **19b** were synthesized from **18a** and **18b**, respectively, by way of the Ichikawa−Isobe rearrangement. Cyclization of the resulting trichloroacetamides **20a** and **20b** prepared by trichloroacetylation of the *N*-allylurethanes using 30 mol % CuCl(bipy) resulted in the desired trichlorinated γ-lactams **21a** (78%) and **21b** (78%), respectively. The structure of trichlorinated γ-lactams **21a** and **21b** was confirmed by transformation (tin-mediated reductive dechlorination and deprotection by Me_3SiI) to the known *cis*-3a-aryloctahydroindol-2-ones **23a** and **23b**, respectively.[18] Synthesis of mesembrane or crinane from **23a** or **23b**, respectively, was reported earlier.[18]

(13) A similar stereochemical outcome was proposed by Ishibashi et al. in the $RuCl_2(PPh_3)_3$-catalyzed cyclization of an analogous system, and the crystal structure unequivocally supported their assignments. Interestingly, the 3,4-dimethoxyphenyl and 3,4-methylenedioxyphenyl homologues, **21a** and **21b**, respectively, exist as a mixture of two conformers. ^{1}H and ^{13}C NMR spectra of **21a** or **21b** at −60 °C showed two sets of signals derived from the conformers. On raising the temperature to 20 °C, extensive broadening of all of the ^{1}H resonances were observed, indicating that interconversion of the conformers occurred at ambient temperature in the NMR time scale. We consider that both the aryl group and the chlorine atom occupy axial positions in one conformer of **21a** or **21b**, whereas those does equatorial positions in the other conformer.

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(15) (a) Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225. (b) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523.

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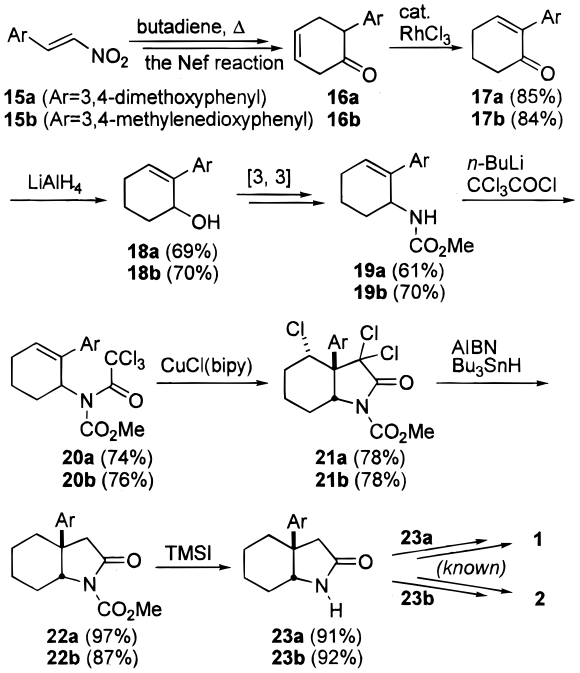
Scheme 5



The Role of the Electron-Withdrawing Group of *N*-Allyltrichloroacetamides in the Cyclization. As reported, the use of the CuCl(bipy) catalyst apparently facilitates activation of a carbon−chlorine bond of *N*-allyltrichloroacetamides compared with the conventional catalysts CuCl in acetonitrile and $RuCl_2(PPh_3)_3$. This is in accord with the fact that treatment of **7a** or **7b** with the CuCl(bipy) catalyst resulted in disappearance of the starting trichloroacetamide within 1 h at room temperature. It is important that smooth cyclization of **7b** proceeded to give **8b** in high yield; this is in sharp contrast to the result that the reaction of **7a** competed with serious side reactions to give a mixture of products. How can we explain this difference?

An interesting observation was reported by Curran and co-workers in the radical cyclization of *N*-allyl α-polyhaloamides:[19] syn-anti rotamer population and its rotational energy barrier are important in the fate of the reaction because the rotational energy barriers of amide C−N bonds (16−22 kcal/mol)[20] are generally higher than 5-exo cyclization (<10 kcal/mol).[19] They found that atom-transfer cyclization of *N*-allyl-*N*-methyliodoacetamide was much more efficient at 80 °C than at 25 °C and proposed that this beneficial effect of temperature arises because an increase in the rate of rotation of the OC−N bond in the intermediate radicals begins to convert syn radicals (which cannot cyclize) to anti radicals (which can cyclize). Recently, Newcomb et al. reported supporting evidence using laser flash photolysis kinetic studies of OC−N bond rotation.[21] Stork and Ishibashi also claimed the importance of the OC−N rotation in the tin-mediated reductive radical cyclization of *N*-allylhaloamides; the cyclization, which occurred from the anti-rotamer, was facilitated by introduction of bulky substituents on the nitrogen atom.[10,22] Since the syn/anti equilibrium is influenced by the steric nature of the group attached to the nitrogen atom, the bulky substituent played an important role in decreasing the percentage of the syn rotamer leading to simple reduction of the *N*-allylhaloamides.

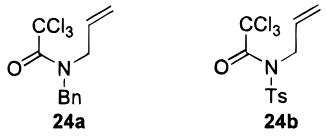


Figure 3.

As model experiments to clarify the effect of CO−N rotation on the fate of the cyclization in our copper-catalyzed system, we carried out variable-temperature NMR studies on *N*-benzyl- and *N*-tosyltrichloroacetamides **24a** and **24b** (Figure 3). The benzyl group is representative of electron-donating groups, whereas the tosyl group is that of electron-withdrawing groups. As shown in Figure 4, ^{1}H NMR of **24a** showed two sets of independent signals derived from the two rotamers at lower than 233 K. Above 233 K, the signals began to broaden, and they coalesced at 308 K. At 343 K, syn-anti interconversion was fast in the NMR time scale, leading to the appearance of only one set of sharp signals. This NMR observation is in accord with the CO−N rotational barrier of 15 kcal/mol reported for *N*,*N*-dimethyltrichloroacetamide. On the other hand, **24b** showed only one set of signals even below at −50 °C, which suggested that amide rotational barrier of the **24b** was much lower than that of **24a**. X-ray structural analyses of **24a** and **24b** also supported the dependence of rotational barrier on the electronic nature of the N substituent.[23]

As mentioned above, the ORTEP view of the bicyclic lactam **8b** suggest a possibly congested transition state for cyclization as illustrated in Scheme 6. Steric repulsion between the phenyl group bound to the C=C bond and the dichloromethyl radical species makes access of the radical species to the C=C bond difficult. Consideration of molecular models suggested the sterically most favor-

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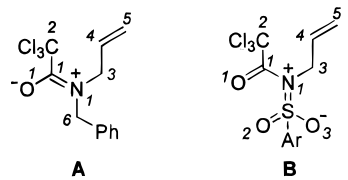
(23) We carried out crystallographic analysis of **24a** and **24b**. The molecular structure of **24a** showed that very effective resonance stabilization provided that six atoms, C2, C1, O1, N1, C3, and C6, lie on the same plane in the molecular structure of **24a**. The C−O distance is substantially longer than the usual C=O distances, whereas the N−CO bond length is shorter than normal N−C single bond distances (N−CO; 1.35 Å (1), C=O.; 1.24 Å (1)). Thus, the N−CO bond of **24a** has a considerable double-bond character like **A**. Since X-ray analysis of **24b** did not converge well (R = 7.7%), precise comparison of the structure of **24b** with that of **24a** is difficult. However, it is noteworthy that the molecular structure suggested a single bond character of N−CO bond (N−CO; 1.375 Å (4), C=O.; 1.195 Å (1)). Five atoms, C1, N1, C3, S1, and O3, lie on the same plane, which makes an angle of 13° with a plane consisting of C2, C1, and O1. We consider that the resonance structure shown as **B** is responsible for facile rotation of the CO−N bond in **24b**.



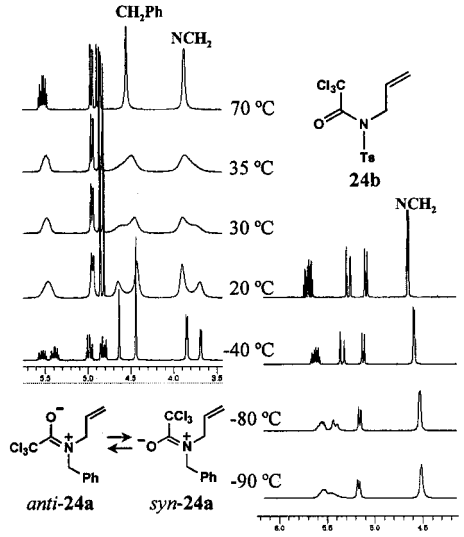
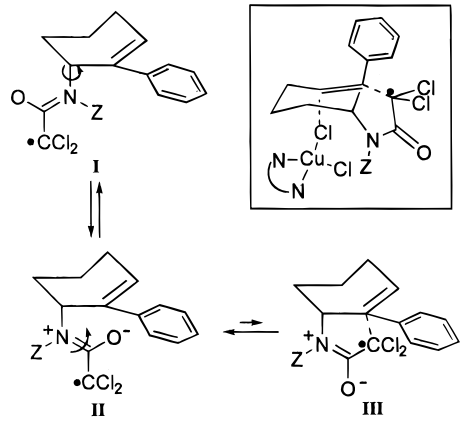


Figure 4. Variable-temperature ^{1}H NMR spectra of *N*-allyltrichloroacetamides **24a** (left) and **24b** (right) in toluene-d_8 solution.

Scheme 6



able conformer of the intermediate radical species to be **I** as shown in Scheme 6. Rotation of the N−C(cyclohexane ring) bond causes the dichloroacetyl moiety to be close to the carbon−carbon double bond; however, rotamer **II** should preferentially exist over **III**, which is suitable for the cyclization. In the case of **7a**, the small *N*-methyl group produces a high population of **I**. Furthermore, the high energy barrier of N−CO rotation resulted in a low population of **III** compared with **II**. This low population of **III** makes the cyclization difficult, and the existence of other reaction pathways from **I** or **II** led to production of a mixture of products. In contrast, alkoxycarbonyl group in **7b** is sterically more bulky than the methyl group in **7a**; this leads to decrease in the population of **I** and an increase in the population of **II** and **III**. More importantly, flexible C−N bond rotation of **7b** facilitates the formation of **III** from **II**, resulting in efficient production of the bicyclic lactams. There may be other reaction pathways from **I** or **II** to a mixture of products; however, free rotation of N−C and N−CO bonds producing **III** predominantly occurs to result in high-yield formation of the cyclization product.

As reported previously, the cyclization of *N*-allyltrichloroacetamides is facilitated by introduction of electron-withdrawing substituents. This is presumably due to the fact that these substituents lower the LUMO of trichloroacetyl moiety and facilitate abstraction of a chlorine atom by the Cu(I) complex via the electron transfer. Usually, this chlorine abstraction is reversible, and hence, cyclization of the *N*-alkyl analogues afforded the product in good yields, though high population of the undesired rotamer makes the reaction slower. A significant difference in the product yield between the reaction of **7a** and **7b** is attributable to the existence of the side reactions, namely those from **I** or **II**. To suppress these reactions, it is important to facilitate the formation of **III** by lowering the N−CO rotational barrier through introduction of the electron-withdrawing substituents.

Conclusion

Cyclization of *N*-alkoxycarbonyl-*N*-(2-aryl-2-cyclohexen-1-yl)trichloroacetamides converted to the corresponding trichlorinated *cis*-3a-aryloctahydroindol-2-ones at room temperature in the presence of CuCl(bipy) catalyst. Introduction of alkoxycarbonyl groups is considered to play an important role in lowering the N−CO rotational barrier, leading to the preferable production of the radical intermediates suitable for the cyclization.[24] The reactions are proved to offer a facile access to alkaloid skeletons such as mesembrines and crinines. Asymmetric synthesis of these alkaloids is now under study by preparing chiral allylic amine derivatives via the Ichikawa−Isobe reaction. Since chirality transfer reaction can generally be achieved by [3.3]sigmatropic rearrangement, we anticipate the chiral *N*-allyltrichloroacetamides can be synthesized from the chiral allylic alcohols such as **18a** and **18b**.

Experimental Section

General Methods. All manipulations were performed under an argon atmosphere unless otherwise noted. Cuprous chloride (CuCl) was prepared from $CuCl_2$ hydrate[25] and stored under a dry argon atmosphere. Purification of 2,2′-bipyridine was made by sublimation. Solvents were distilled under an inert atmosphere from CaH_2 (CH_2Cl_2, MeCN), sodium/benzophenone (THF, toluene), or magnesium tunings (EtOH). The solvent used for the cyclization was degassed by three freeze−pump−thaw cycles just before use. 2-Phenyl-2-cyclohexen-1-ol (**3**)[11] and 6-aryl-3-cyclohexen-1-ones (**16a)** and (**16b)** were prepared by the procedure in the literature.[15] Transformation of **3**, **16a**, and **16b** to the corresponding N-substituted 2-aryl-2-cyclohexenylamines was described in the Supporting Information. Column chromatography was carried out using silica gel (Merck No. 1.07734.9025 or Wakogel FC-40). Thin-layer chromatography was carried out with silica gel 60 F_{254} (Merck).

***N*-Methyl-*N*-(2-phenyl-2-cyclohexen-1-yl)trichloroacetamide (7a).** To a solution of *N*-methyl-*N*-(2-phenyl-2-cyclohexen-1-yl)amine (661 mg, 3.5 mmol) in Et_2O (12 mL) was added triethylamine (1.28 mL, 7.1 mmol) at room temperature. Trichloroacetyl chloride (800 μL, 7.1 mmol) was then added at 0 °C, and the mixture was stirred at room temperature for 3 h. The resulting mixture was treated with 2 N HCl, stirred for an additional 10 min, and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (silica gel, eluent: 10% Et_2O/hexane) to give **7a** (1.09 g, 80% from **4**) as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.31−7.18 (m, 5H), 6.30 (m, 1H), 5.78 (m, 1H), 2.89 (s, 3H), 2.32−2.21 (m, 2H), 2.14−2.07 (m, 1H), 1.91−1.83 (m, 1H),

(24) The importance of the electron-withdrawing group on the nitrogen atom has recently reported by Giese et al. in the photocyclization of *o*-aminophenyl ketones: Seiler, M.; Schumacher, A.; Lindemann, U.; Barbosa, F.; Giese B. *Synlett* **1999**, 1588.

(25) Keller, R. N.; Wycoff, H. D. *Inorg. Synth.* **1946**, *2*, 1.

1.83−1.74 (m, 2H); ^{13}C NMR ($CDCl_3$) 160.50, 139.38, 137.21, 131.83, 128.39, 127.20, 125.48, 93.52, 55.08, 32.72, 26.37, 25.62, 20.88; IR (CH_2Cl_2) 1668 cm^{-1}; FAB-MS *m*/*z* 336 (MH^+ + 4), 334 (MH^+ + 2), 332 (MH^+). Anal. Calcd for $C_{15}H_{16}NOCl_3$: C, 54.16; H, 4.85; N, 4.21. Found: C, 54.13; H, 4.89; N, 4.07.

General Procedure for the Preparation of *N*-(Alkoxycarbonyl)-*N*-(2-aryl-2-cyclohexen-1-yl)trichloroacetamides 7b, 11, 20a, and 20b. In a typical example, to a solution of **10** (278 mg, 1.20 mmol) and 2,2′-bipy (trace, as indicator) in 12 mL of THF was added dropwise a hexane solution of *n*-BuLi (1.54 M, 840 μL) at −45 °C. The mixture was stirred at the same temperature for 10 min and at 0 °C for 10 min. Trichloroacetyl chloride (145 μL, 1.30 mmol) was added to the solution, and the mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O. The combined organic layers were washed with a 1 N NaOH aqueous solution and brine successively, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography (silica gel, eluent: 12% Et_2O/hexane) to give the trichloroacetamide **11** (392 mg, 87%) as a colorless solid**.**

***N*-(Benzyloxycarbonyl)-*N*-(2-phenyl-2-cyclohexen-1-yl)-trichloroacetamide (7b):** colorless solid; 66% yield; mp 71−73 °C; ^{1}H NMR ($CDCl_3$) 7.35−7.31 (m, 3H), 7.28−7.17 (m, 7H), 6.09 (m, 1H), 5.54 (m, 1H), 5.15 (br, 1H), 5.01 (d, J = 12 Hz, 1H), 2.32−2.05 (m, 4H), 1.96−1.88 (m, 1H), 1.78−1.65 (m, 1H); ^{13}C NMR ($CDCl_3$) 165.49, 152.98, 138.91, 136.21, 133.72, 130.59, 128.99, 128.77, 128.46, 128.21, 127.17, 126.43, 93.01, 69.53, 58.31, 27.96, 25.29, 21.30; IR (CH_2Cl_2) 1753, 1707 cm^{-1}; FAB-MS *m*/*z* 456 (MH^+ + 4), 454 (MH^+ + 2), 452 (MH^+); FAB-HRMS calcd for $C_{22}H_{20}NO_3Cl_3$ + H 452.0587, found 452.0603.

***N*-(Methoxycarbonyl)-*N*-(2-phenyl-2-cyclohexen-1-yl)-trichloroacetamide (11):** colorless solid; 87% yield; mp 93−95 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$) 7.34−7.17 (m, 5H), 6.13 (m, 1H), 5.52 (m, 1H), 3.70 (s, 3H), 2.38−2.08 (m, 4H), 2.00−1.90 (m, 1H), 1.80−1.66 (m, 1H); ^{13}C NMR ($CDCl_3$) 165.42, 153.68, 138.91, 136.06, 130.81, 128.24, 127.24, 126.56, 93.14, 58.26, 53.77, 27.92, 25.36, 21.32; IR (CH_2Cl_2) 1759, 1709 cm^{-1}; FAB-MS *m*/*z* 380 (MH^+ + 4), 378 (MH^+ + 2), 376 (MH^+). Anal. Calcd for $C_{16}H_{16}NO_3Cl_3$: C, 51.02; H, 4.28; N, 3.72. Found: C, 51.37; H, 4.45; N, 3.70.

***N*-(Methoxycarbonyl)-*N*-[2-(3,4-dimethoxyphenyl)-2-cyclohexen-1-yl]trichloroacetamide (20a):** colorless solid; 74% yield; mp 126−128 °C; ^{1}H NMR ($CDCl_3$) 6.86−6.82 (m, 2H), 6.77 (d, J = 9 Hz, 1H), 6.09 (m, 1H), 5.50 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.68 (brs, 3H), 2.37−2.16 (m, 3H), 2.15−2.05 (m, 1H), 2.00−1.90 (m, 1H), 1.79−1.66 (m, 1H); ^{13}C NMR ($CDCl_3$) 165.28, 153.64, 148.47, 148.28, 135.49, 131.82, 129.86, 118.94, 110.91, 109.67, 93.21, 58.32, 55.89, 55.69, 53.72, 28.04, 25.25, 21.28; IR (CH_2Cl_2) 1759, 1708 cm^{-1}; FAB-MS *m*/*z* 439 (M^+ + 4), 437 (M^+ + 2), 435 (M^+), 217; FAB-HRMS calcd for $C_{18}H_{20}NO_5Cl_3$ 435.0407, found 435.0400.

***N*-(Methoxycarbonyl)-*N*-[2-(3,4-methylenedioxyphenyl)-2-cyclohexen-1-yl]trichloroacetamide (20b):** colorless oil; 76% yield; ^{1}H NMR ($CDCl_3$) 6.77 (d, J = 2 Hz, 1H), 6.74 (dd, J = 8, 2 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.04 (m, 1H), 5.91 (d, J = 1 Hz, 1H), 5.90 (d, J = 1 Hz, 1H), 5.42 (m, 1H), 3.73 (brs, 3H), 2.36−2.04 (m, 4H), 1.99−1.88 (m, 1H), 1.79−1.64 (m, 1H); ^{13}C NMR ($CDCl_3$) 165.38, 153.63, 147.45, 146.74, 135.48, 133.13, 130.11, 120.02, 108.04, 107.39. 100.83, 93.16, 58.38, 53.79, 27.90, 25.27, 21.22; IR (CH_2Cl_2) 1760, 1709 cm^{-1}; FAB-MS *m*/*z* 423 (M^+ + 4), 421 (M^+ + 2), 419 (M^+), 200; HRMS calcd for $C_{17}H_{16}NO_5Cl_3$ 419.0094. found 419.0096.

General Procedure for the CuCl(bipy)-Catalyzed Cyclization of Trichloroacetamides 7a,b, 11, and 20a,b. In a typical example, CuCl (20.8 mg, 0.21 mmol) and **20a** (308 mg, 0.71 mmol) were measured into a 20 mL flask. The atmosphere was replaced carefully by argon and degassed dichloromethane (3 mL) was added. Then, a solution of 2,2′-bipyridine (32.8 mg in 1 mL of CH_2Cl_2, 0.21 mmol) was added, and the mixture was stirred at room temperature for 1 h. The resulting mixture was transferred to the head of a short pad of silica gel and eluted with Et_2O. The eluent was concentrated, and the residue was purified by chromatography (silica gel, eluent: 30% Et_2O/hexane) to give the lactam **21a** (241 mg, 78%) as a colorless solid.

3,3,4-Trichloro-1-methyl-3a-phenyl-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (8a): colorless solid; 20% yield; mp 210−211 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$) 7.95 (d, J = 8 Hz, 1H), 7.51−7.46 (m, 1H), 7.45−7.39 (m, 2H), 7.34−7.29 (m, 1H), 4.90 (m, 1H), 4.51 (m, 1H), 3.00 (s, 3H), 2.39−2.31 (m, 1H), 2.17−2.09 (m, 1H), 2.04−1.94 (m, 1H), 1.89−1.82 (m, 1H), 1.60−1.47 (m, 2H); ^{13}C NMR ($CDCl_3$) 166.70, 136.56, 129.27, 128.72, 128.51, 127.66, 126.72, 90.88, 62.16, 57.12, 55.46, 30.11, 27.47, 22.09, 14.84; IR (CH_2Cl_2) 1729 cm^{-1}; FAB-MS *m*/*z* 336 (MH^+ + 4), 334 (MH^+ + 2), 332 (MH^+). Anal. Calcd for $C_{15}H_{16}NOCl_3$: C, 54.16; H, 4.85; N 4.21. Found: C, 54.26; H, 4.90; N 4.17.

1-(Benzyloxycarbonyl)-3,3,4-trichloro-3a-phenyl-2,3,-3a,4,5,6,7,7a-octahydroindol-2-one (8b): colorless solid; 83% yield; mp 210.5−212 °C (CH_2Cl_2/cyclohexane); ^{1}H NMR ($CDCl_3$) 7.91 (br, 1H), 7.51−7.32 (m, 9H), 5.46 (d, J = 13 Hz, 1H), 5.36 (d, J = 13 Hz, 1H), 5.02 (m, 1H), 4.98 (m, 1H), 2.92 (m, 1H), 2.09−1.94 (m, 2H), 1.87 (m, 1H), 1.55−1.45 (m, 2H); ^{13}C NMR ($CDCl_3$, −30 °C) 165.29, 151.27, 134.96, 134.47, 129.24, 128.98, 128.72, 128.58, 128.28, 127.50, 127.42, 126.40, 89.42, 68.94, 62.08, 55.21, 54.79, 29.97, 21.57, 14.29; IR (CH_2Cl_2) 1802, 1777, 1734 cm^{-1}; FAB-MS *m*/*z* 456 (MH^+ + 4), 454 (MH^+ + 2), 452 (MH^+). Anal. Calcd for $C_{22}H_{20}NO_3Cl_3$: C, 58.36; H, 4.45; N, 3.09. Found: C, 58.42; H, 4.52; N, 3.05.

3,3,4-Trichloro-1-(methoxycarbonyl)-3a-phenyl-2,3,-3a,4,5,6,7,7a-octahydroindol-2-one (12): colorless solid; 88% yield; mp 150.5−152.5 °C (Et_2O/hexane); ^{1}H NMR ($CDCl_3$) 7.92 (m, 1H), 7.56−7.33 (m, 4H), 5.03 (m, 1H), 4.99 (m, 1H), 3.98 (s, 3H), 2.93 (m, 1H), 2.14−1.95 (m, 2H), 1.94−1.83 (m, 1H), 1.59−1.45 (m, 2H); ^{13}C NMR ($CDCl_3$) 165.04, 152.19, 135.45, 129.32, 129.02, 128.75, 127.68, 126.63, 89.68, 62.16, 55.40, 55.09, 54.40, 30.17, 22.04, 14.53; IR (CH_2Cl_2) 1804, 1776, 1739 cm^{-1}; FAB-MS *m*/*z* 380 (MH^+ + 4), 378 (MH^+ + 2), 376 (MH^+); FAB-HRMS calcd for $C_{16}H_{16}NO_3Cl_3$ + H 376.0274, found 376.0274.

3,3,4-Trichloro-1-(methoxycarbonyl)-3a-(3,4-dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (21a): colorless solid; 78% yield; mp 194−196 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$) 7.51−7.35 (m, 1H), 7.01−6.78 (m, 2H), 4.97−4.89 (m, 2H), 3.98 (s, 3H), 3.94 (brs, 3H), 3.92 (s, 3H), 3.02−2.85 (m, 1H), 2.16−1.94 (m, 2H), 1.93−1.83 (m, 1H), 1.68−1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, −60 °C) 165.60, 165.55, 152.03, 151.91, 148.52, 148.38, 148.34, 147.86, 126.96, 126.83, 120.14, 119.18, 110.77, 109.79, 109.66, 108.22, 89.81, 89.66, 62.30, 62.18, 55.95, 55.91, 55.87, 55.74, 55.39, 55.32, 55.04, 54.97, 54.33, 54.25, 29.84, 29.79, 21.73, 21.50, 14.35, 14.29; IR (CH_2Cl_2) 1804, 1777, 1738 cm^{-1}; FAB-MS *m*/*z* 440 (MH^+ + 4), 438 (MH^+ + 2), 436 (MH^+); FAB-HRMS calcd for $C_{18}H_{20}NO_5Cl_3$ + H 436.0485, found 436.0479.

3,3,4-Trichloro-1-(methoxycarbonyl)-3a-(3,4-methylenedioxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (21b): colorless solid; 78% yield; mp 217−219 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$) 7.45−7.33 (m, 1H), 6.95−6.77 (m, 2H), 6.04 (s, 2H), 4.98−4.79 (m, 2H), 3.98 (s, 3H), 2.99−2.79 (m, 1H), 2.12−1.79 (m, 4H), 1.65−1.45 (m, 2H); ^{13}C NMR ($CDCl_3$, −60 °C) 165.50, 151.76, 148.02, 147.68, 147.35, 128.23, 128.09, 121.30, 120.32, 108.84, 108.15, 107.90, 106.66, 101.68, 101.59, 89.69, 89.35, 62.29, 62.07, 55.43, 54.88, 54.37, 54.19, 29.74, 29.65, 21.27, 14.23, 14.19; IR (CH_2Cl_2) 1806, 1778, 1738 cm^{-1}; FAB-MS *m*/*z* 424 (MH^+ + 4), 422 (MH^+ + 2), 420 (MH^+); FAB-HRMS calcd for $C_{17}H_{16}NO_5Cl_3$ + H, 420.0172, found 420.0168.

General Procedure for the Tin-mediated Dechlorination of γ-Lactams 12 and 21a,b. In a typical example, to a solution of **12** (126 mg, 0.335 mmol) and AIBN (22 mg, 0.134 mmol) in 10 mL of toluene was added tributyltin hydride (370 μL, 1.38 mmol), and the mixture was heated under reflux for 3 h. After being cooled to room temperature, the solvent was removed under reduced pressure. The residue was purified by chromatography (silica gel, eluent: 30% EtOAc/hexane) to give **13** (72 mg, 79%) as a colorless solid.

1-(Methoxycarbonyl)-3a-phenyl-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (13): mp 99−100.5 °C; ^{1}H NMR ($CDCl_3$)

7.30−7.23 (m, 4H), 7.20−7.13 (m, 1H), 4.44 (dd, J = 10, 6 Hz, 1H), 3.73 (s, 3H), 2.94 (d, J = 17 Hz, 1H), 2.66 (d, J = 17 Hz, 1H), 2.38−2.28 (m, 1H), 1.97−1.87 (m, 1H), 1.79−1.57 (m, 3H), 1.49−1.21 (m, 3H); ^{13}C NMR ($CDCl_3$) 172.32, 151.95, 145.55, 128.71, 126.83, 125.57, 61.53, 53.37, 43.12, 41.36, 35.54, 28.52, 22.37, 21.88; IR (CH_2Cl_2) 1784, 1752, 1722 cm^{-1}; EI-MS m/z 273 (M^+); HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1365.

1-(Methoxycarbonyl)-3a-(3,4-dimethoxyphenyl)-2,3,-3a,4,5,6,7,7a-octahydroindol-2-one (22a): colorless oil; 97% yield; ^{1}H NMR ($CDCl_3$) 6.89 (dd, J = 8, 2 Hz, 1H), 6.84 (d, J = 2 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 4.45 (dd, J = 10, 6 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H), 3.00 (d, J = 17 Hz, 1H), 2.70 (d, J = 17 Hz, 1H), 2.45−2.35 (m, 1H), 2.03−1.93 (m, 1H), 1.84−1.66 (m, 3H), 1.55−1.30 (m, 3H); ^{13}C NMR ($CDCl_3$) 172.46, 152.13, 149.07, 147.96, 138.21, 117.79, 111.15, 109.43, 61.96, 55.95, 55.88, 53.48, 43.01, 41.62, 35.66, 28.68, 22.52, 21.01; IR (CH_2Cl_2) 1784, 1746, 1721 cm^{-1}; EI-MS m/z 333 (M^+); HRMS calcd for $C_{18}H_{23}NO_5$ 333.1576, found 333.1575.

1-(Methoxycarbonyl)-3a-(3,4-methylenedioxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (22b): colorless solid; 87% yield; mp 121−123 °C; ^{1}H NMR ($CDCl_3$) 6.84 (d, J = 2 Hz, 1H), 6.79 (dd, J = 8, 2 Hz, 1H), 6.75 (d, J = 8 Hz, 1H), 5.95 (s, 2H), 4.41 (dd, J = 10, 6 Hz, 1H), 3.82 (s, 3H), 2.98 (d, J = 17 Hz, 1H), 2.65 (d, J = 17 Hz, 1H), 2.44−2.34 (m, 1H), 2.00−1.90 (m, 1H), 1.82−1.65 (m, 3H), 1.53−1.28 (m, 3H); ^{13}C NMR ($CDCl_3$) 172.32, 152.08, 148.18, 146.40, 139.69, 118.67, 108.15, 106.63, 101.18, 62.01, 53.49, 43.23, 41.64, 35.84, 28.66, 22.48, 22.02; IR (CH_2Cl_2) 1784, 1746, 1721 cm^{-1}; EI-MS m/z 317 (M^+); HRMS calcd for $C_{17}H_{19}NO_5$ 317.1263, found 317.1261.

General Procedure for the TMSI-Mediated Deprotection of the γ-Lactams 13 and 22a,b. In a typical example, to a solution of **13** (242 mg, 0.89 mmol) in dichloromethane (8 mL) was added iodotrimethylsilane (630 μL, 4.4 mmol), and the mixture was heated under reflux for 2 h. After the mixture was cooled to room temperature, MeOH (0.5 mL) was added, and after concentration, Et_2O (40 mL) and a 1 N aqueous HCl solution (20 mL) were added. The organic layer was separated, and the aqueous layer was neutralized with a 4 N aqueous NaOH solution at 0 °C and extracted with dichloromethane (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give **14** (192 mg, 100%) as a yellow oil.

3a-Phenyl-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (14): ^{1}H NMR ($CDCl_3$) 7.39−7.22 (m, 5H), 5.84 (br, 1H), 4.24 (t, J = 3 Hz, 1H), 2.59 (d, J = 16 Hz, 1H), 2.49 (d, J = 16 Hz, 1H), 2.04−1.80 (m, 4H), 1.62−1.46 (m, 3H), 1.29−1.14 (m, 1H); ^{13}C NMR ($CDCl_3$) 176.83, 144.55, 128.47, 126.51, 126.39, 56.76, 48.41, 45.34, 35.09, 26.62, 21.15, 19.89; IR (CH_2Cl_2) 3425, 1698 cm^{-1}; EI-MS m/z 215 (M^+); HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1310.

***cis*-3a-(3,4-Dimethoxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (23a):** pale yellow solid; 91% yield; mp 144−146 °C (lit.[18a] 149−151 °C); ^{1}H NMR ($CDCl_3$) 6.89 (dd, J = 8, 2 Hz, 1H), 6.84 (d, J = 8 Hz, 1H), 6.83 (d, J = 2 Hz, 1H), 6.18 (br, 1H), 4.22 (t, J = 3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.59 (d, J = 16 Hz, 1H), 2.45 (d, J = 16 Hz, 1H), 2.01−1.93 (m, 1H), 1.91−1.76 (m, 3H), 1.61−1.46 (m, 3H), 1.30−1.17 (m, 1H); ^{13}C NMR/DEPT ($CDCl_3$) 176.29 (C), 148.88 (C), 147.59 (C), 137.02 (C), 118.67 (CH), 110.85 (CH), 110.25 (CH), 56.85 (CH), 56.00 (CH_3), 55.87 (CH_3), 48.49 (CH_2), 45.03 (C), 34.86 (CH_2), 26.73 (CH_2), 21.27 (CH_2), 19.91 (CH_2); IR (CH_2Cl_2) 3425, 1699 cm^{-1}; EI-MS m/z 275 (M^+); HRMS calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1518.

***cis*-3a-(3,4-Methylenedioxyphenyl)-2,3,3a,4,5,6,7,7a-octahydroindol-2-one (23b):** slightly yellow solid; 92% yield; mp 145−147 °C (lit.[18b] 142−144 °C); ^{1}H NMR ($CDCl_3$) 6.81 (m, 1H), 6.78 (m, 2H), 5.96 (s, 2H), 5.90 (br, 1H), 4.16 (t, J = 3 Hz, 1H), 2.54 (d, J = 16 Hz, 1H), 2.42 (d, J = 16 Hz, 1H), 1.95−1.77 (m, 4H), 1.61−1.45 (m, 3H), 1.29−1.14 (m, 1H); ^{13}C NMR/DEPT ($CDCl_3$) 176.40 (C), 147.84 (C), 145.87 (C), 138.49 (C), 119.47 (CH), 107.96 (CH), 107.34 (CH), 101.06 (CH_2), 56.78 (CH), 48.60 (CH_2), 45.21 (C), 35.14 (CH_2), 26.55 (CH_2), 21.13 (CH_2), 19.89 (CH_2); IR (CH_2Cl_2) 3425, 1701 cm^{-1}; EI-MS m/z 259 (M^+); Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.37; H, 6.63; N, 5.39.

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Supporting Information Available: Experimental details including those for the preparation of 2-aryl-2-cyclohexylamine derivatives. Crystallographic data and ORTEP drawings for **8b**, **24a**, and **24b** and copies of ^{1}H and ^{13}C NMR spectra of all compounds lacking elemental analysis (**4**, **5**, **7b**, **12**−**14**, **17a**, **20a**,**b**−**22a**,**b**, **23a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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