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# Pd(II)-SPRIX catalyzed enantioselective construction of pyrrolizines/pyrroloindoles employing molecular oxygen as the sole oxidant

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ABSTRACT

Pd(II)-SPRIX catalyst coupled with an environmentally benign molecular oxygen as the sole oxidant successfully exploited the construction of pyrrolizines/pyrroloindoles, imperative scaffolds of bio-potent molecules through intramolecular C—N and C—C bond forming reactions in good yields with appreciable enantioselectivities.

## 1. Introduction

Palladium catalyzed oxidation reactions play vital roles in the construction of biopertinent organic targets via heteroatom incorporation and/functional group manipulation.[1] Despite significant developments in this area, Pd(II) catalysis employing molecular oxygen as the sole oxidant is particularly advantageous because molecular oxygen is not only an inexpensive and environmentally benign one but also helps in facilitating product purification. Further, the use of organic oxidants or cocatalysts, for instance benzoquinone or copper salts, respectively, to regenerate Pd (II) species from Pd(0) in oxidative Pd(II) catalysis might impede the development of efficient asymmetric transformations. Over the past decade, significant progress has been made in oxidation catalysis exploiting Pd(II) coupled with molecular oxygen as the sole oxidant.[2] Although various chiral ligands have been reported in Pd (II) catalysis along with molecular oxygen in search for efficient aerobic asymmetric processes,[3] revealing new classes of chiral ligands for such aerobic asymmetric processes is highly indispensable. Spiro bis(isoxazoline) ligands (SPRIXs), developed by our group,[4] are a class of chiral ligands, which promote various Pd catalyzed asymmetric processes[5] including recent examples, such as Wacker-type cyclization of geranylphenols[6]/2-alkenyl-1,3-diketones,[7] aminocarbonylation of alkenylureas,[8] and oxidative cyclization of enynes.[9] Notably, in all the cases, either benzoquinone or bis(acetoxy)iodobenzene has been utilized as the stoichiometric oxidant. Disclosed herein is a successful utilization of Pd (II)-SPRIX catalyst coupled with molecular oxygen as the sole oxidant in an enantioselective construction of pyrrolizines/pyrroloindoles, pertinent scaffolds of bio-important targets,[10,11] via intramolecular C—N and C—C bond forming reactions.

## 2. Results and discussion

Initially, the optimization of the reaction was grouped for which **1a** was chosen as a model substrate. It was hypothesized that a critical choice of Pd (II) source along with an appropriate oxidant in addition to a chiral SPRIX ligand might efficiently catalyze the enantioselective construction of **2a** through intramolecular C—N and C—C bond formations (Scheme 1). A preliminary examination showed that Pd(TFA)$_2$ and (*M*,*S*,*S*)-*i*-Pr-SPRIX [10 mol % and 40 mol %, respectively (1:4)] along with molecular oxygen (1 atm) as the sole oxidant in toluene at 50 °C for 24 h effectively catalyzed the model reaction to produce **2a** in 26% yield with 25% ee. It should be noted that there were no side products formed during the reaction and 69% of the starting material was recovered (Table 1, entry 1). To our delight, addition of molecular sieves (25 mg) unless otherwise identical conditions significantly enhanced not only the yield but also the enantioselectivity (entry 2). Having the utility of molecular sieves as one of the common moisture trapping agents in

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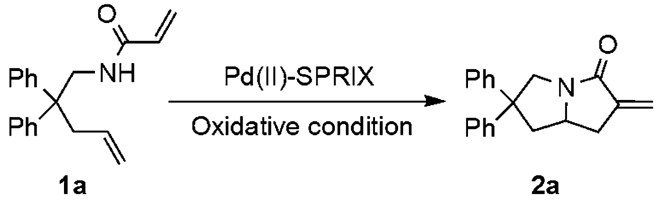


**Scheme 1.** Enantioselective synthesis of model, 2-methylene-6,6-diphenyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one (**2a**).

**Table 1**
Effect of (*M,S,S*)-*i*-Pr-SPRIX and molecular sieves [a]

| Entry | Pd(II)-SPRIX (mol %) | MS 3 Å (mg)[b] | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 10–40 | — | 26 | 25 |
| 2 | 10–40 | 25 | 34 | 52 |
| 3 | 20–80 | 25 | 43 | 32 |
| 4 | 10–20 | 25 | 37 | 55 |
| 5 | 10–15 | 25 | 36 | 56 |
| 6 | 10–12 | 25 | 33 | 53 |
| 7 | 10–15 | 50 | 35 | 50 |
| 8 | 10–15 | 100 | 28 | 34 |

[a] All the yields were isolated ones; all the ee were determined by HPLC analysis; the reaction time was 24 h.

[b] Amount of MS 3 Å (mg/0.05 mmol substrate).

a chemical reaction in mind, other dehydrating agents, such as anhydrous magnesium sulfate ($MgSO_4$) and anhydrous sodium sulfate ($Na_2SO_4$) were also screened in place of molecular sieves, however, the results were inferior compared to molecular sieves. Further, the use of benzoquinone (1 equiv) as oxidant afforded a double bond isomerized product **2a**′ (28% yield with 43% ee) along with the desired **2a** (32% yield and 41% ee).[12] Tuning the $Pd(TFA)_2$ and (*M,S,S*)-*i*-Pr-SPRIX ratio to 1:1.5 further increased the yield and enantioselectivity (entry 5) while 2:8, 1:2, and 1:1.2 ratios of $Pd(TFA)_2$ and (*M,S,S*)-*i*-Pr-SPRIX afforded the model lower in yield as well as enantioselectivity (entries 3, 4, and 6). Besides, increasing the amount of molecular sieves exhibited no significant development in both the yield as well as the enantioselectivity (entries 7 and 8).

Additionally, various Pd(II) sources were screened to investigate whether counter ions have impact on the yield and/or the enantioselectivity of **2a** but none of the other tested Pd(II) sources furnished either better yield or enantioselectivity and infact afforded much lower yields and enantioselectivities (Table 2, entries 2–6). Although the effect of MS 3 Å and TFA counter ions had major impacts on the yield and the enantioselectivity of **2a**, the scrupulous reason for the remarkable effects is yet to be known.

**Table 2**
Effect of Pd(II) source, solvent, temperature, and reaction time [a]

| Entry | Pd(II) source | Solvent | Temp (°C) | Yield [b] (%) | ee [c] (%) |
|---|---|---|---|---|---|
| 1 | $Pd(TFA)_2$ | Toluene | 50 | 36 | 56 |
| 2 | $Pd(OAc)_2$ | Toluene | 50 | 12 | 15 |
| 3 | $PdCl_2$ | Toluene | 50 | 13 | 12 |
| 4 | $Pd(hfacac)_2$ | Toluene | 50 | 8 | 10 |
| 5 | $Pd(MeCN)_2Cl_2$ | Toluene | 50 | 16 | 4 |
| 6 | $Pd(PhCN)_2Cl_2$ | Toluene | 50 | 10 | 14 |
| 7 | $Pd(TFA)_2$ | DMF | 50 | 39 | *rac* |
| 8 | $Pd(TFA)_2$ | Diglyme | 50 | 12 | 4 |
| 9 | $Pd(TFA)_2$ | MeCN | 50 | 16 | 32 |
| 10 | $Pd(TFA)_2$ | DCE | 50 | 24 | 12 |
| 11 | $Pd(TFA)_2$ | MeOH | 50 | 9 | 8 |
| 12 | $Pd(TFA)_2$ | 1,4-Dioxane | 50 | 40 | 38 |
| 13 | $Pd(TFA)_2$ | Toluene | 70 | 42 | 60 |
| 14 | $Pd(TFA)_2$ | Toluene | 80 | 41 | 60 |
| 15 | $Pd(TFA)_2$ | Toluene | 70 | 76 [d] | 60 |

[a] Reaction conditions: Pd source (10 mol %), (*M,S,S*)-*i*-Pr-SPRIX (15 mol %), MS 3 Å (25 mg/0.05 mmol substrate), solvent (0.5 mL), $O_2$ (1 atm), 24 h.

[b] All the yields were isolated ones.

[c] All the ee were determined by HPLC analysis.

[d] After prolonged reaction time (120 h).

The attention was then focused toward the effect of solvent on the yield and the enantioselectivity of **2a** (Table 2, entries 7–12). Use of *N*,*N*-dimethylformamide (DMF) resulted in slightly higher yield but with a complete loss of enantioselectivity by affording a racemic **2a**. Screening with diglyme, acetonitrile (MeCN), 1,2-dichloroethane (DCE), and methanol (MeOH) accomplished in lower both yields as well as enantioselectivities while 1,4-dioxane afforded in slightly higher yield though with less enantioselectivity. Besides, increasing the temperature from 50 °C to 70 °C provided in slightly higher both yield as well as enantioselectivity (Table 2, entry 13) while neither yield nor enantioselectivity improved when the temperature was further increased to 80 °C (Table 2, entry 14). At 70 °C, the acceleration of the reaction to provide the improved yield is due probably to the increased solubility of oxygen in toluene[13] and the reason for the slightly improved enantioselectivity is yet to be known (Table 2, entry 1 vs entry 13). Noteworthy is that prolonged reaction period at 70 °C afforded **2a** in better yield albeit with no deprivation in enantioselectivity (Table 2, entry 15).

Having the unique reactivity of SPRIX coupled with Pd sources for various enantioselective reactions due to their relatively greater Lewis acidity of the Pd-SPRIX complex[14] in mind, various chiral ligands were screened in place of (*M,S,S*)-*i*-Pr-SPRIX. As depicted in Table 3, none of the ligands coupled with $Pd(TFA)_2$ efficiently

**Table 3**
Effect of chiral ligand and additive [a]

| Entry | Chiral ligand | Additive (2 equiv) | Yield [b](%) | ee [c](%) |
|---|---|---|---|---|
| 1 | **3** | — | 42 | 60 |
| 2 | **4** | — | — | — |
| 3 | **5** | — | $<5$ | ND |
| 4 | **6** | — | — | — |
| 5 | **7** | — | 12 | 14 |
| 6 | **8** | — | — | — |
| 7 | **9** | — | — | — |
| 8 | **10** | — | — | — |
| 9 | **3** | DIPEA | 46 | 26 |
| 10 | **3** | DIPEA[d] | 45 | 27 |
| 11 | **3** | $Et_3N$ | 40 | 20 |
| 12 | **3** | NaOAc | 33 | 30 |
| 13 | **3** | KOAc | 35 | 28 |
| 14 | **3** | $Na_2CO_3$ | 47 | 52 |

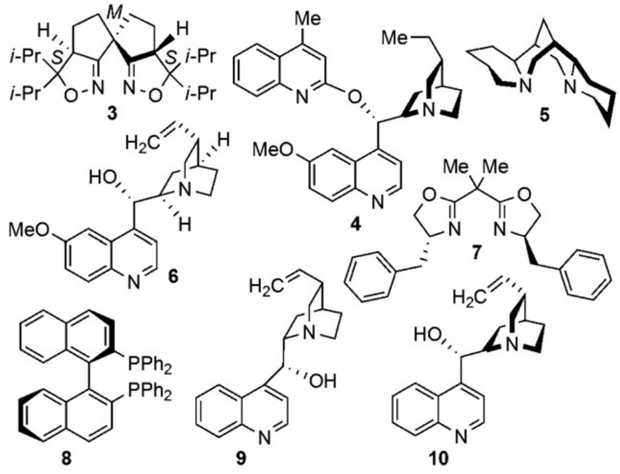
ND: Not determined.

[a] Reaction conditions: $Pd(TFA)_2$ (10 mol %), Chiral ligand (15 mol %), MS 3 Å (25 mg/0.05 mmol substrate), toluene (0.5 mL), $O_2$ (1 atm), 24 h.

[b] All the yields were isolated ones.

[c] All the ee were determined by HPLC analysis.

[d] DIPEA (1 equiv) was added.

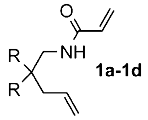
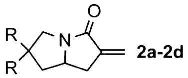
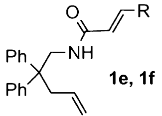
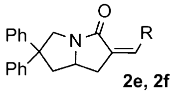
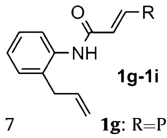
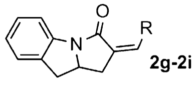
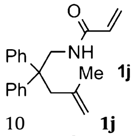
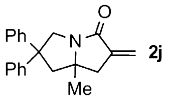
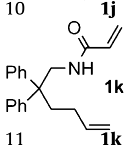
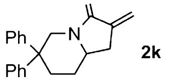


promoted the enantioselective construction of **2a** and notably the reaction was inefficient even with the use of higher loading of **5**[3e] (40 mol %) as it provided only trace amount of **2a** with the recovery of most of the starting material **1a** (85%).

Further, additive effects on the model reaction were studied (Table 3, entries 9–14). Although addition of Hünig's base (DIPEA) and sodium carbonate ($Na_2CO_3$) slightly improved the yield of **2a**, the enantioselectivities were unfortunately decreased (entries 9, 10, and 14). Likewise, addition of triethyl amine ($Et_3N$), sodium acetate (NaOAc), and potassium acetate (KOAc) enhanced neither the yield nor the enantioselectivity (entries 11–13). Thus, 10 mol % of $Pd(TFA)_2$, 15 mol % of (*M*,*S*,*S*)-*i*-Pr-SPRIX, and MS 3 Å in toluene at 70 °C under $O_2$ (1 atm) for 120 h is the optimal conditions for the enantioselective construction of **2a** from **1a**.

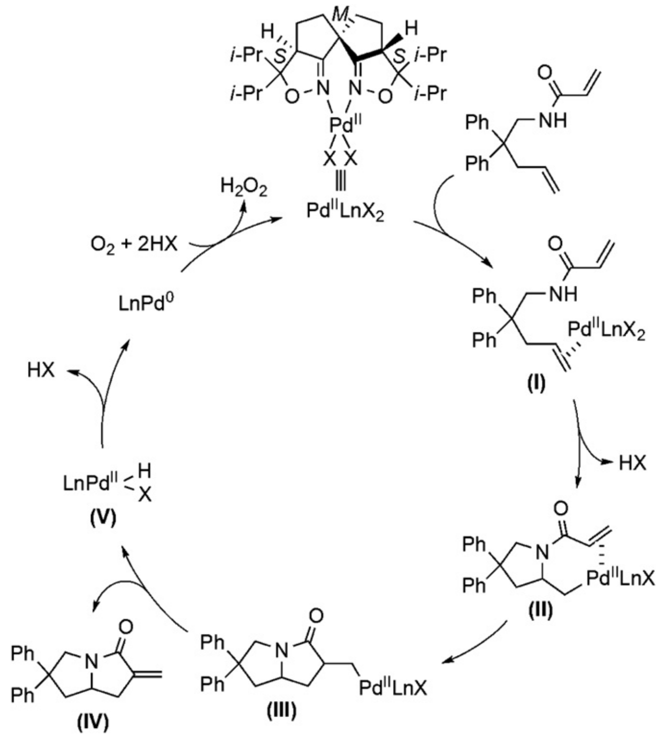
To illustrate the general applicability of the model reaction, a diverse range of substrates were examined and the results are shown in Table 4. Replacing sterically bulky *gem*-diphenyl groups of **1a** by a less bulky *gem*-dimethyl group (i.e., **1b**) produced its corresponding pyrrolizine **2b** in comparable yield; however, a considerable reduction in enantioselectivity was perceived (entry 2). Switching over to the use of cyclopentyl and cyclohexyl substituted substrates (**1c** and **1d**, respectively) in place of *gem*-diphenyl substituted substrate (**1a**) also delivered their corresponding pyrrolizines **2c** and **2d**, respectively, in good to better yields despite their lower enantioselectivities (entries 3 and 4). Further, *N*-cinnamoyl and *N*-(2-chlorocinnamoyl) substituted substrates with (*E*)-configuration did not provide their corresponding pyrrolizines **2e** and **2f**, respectively (entries 5 and 6). It should be noted that most of the starting materials of **1e** and **1f** were consumed during the reaction; however, unidentified mixture of products were obtained. Lowering the reaction temperature to 50 °C and 25 °C unless otherwise identical conditions also provided no required targets, considerable amounts of starting materials were recovered instead (15% of **1e** and <10% of **1f** at 50 °C as well as 40% of **1e** and 25% of **1f** at 25 °C). In contrast, (*E*)-configured substrate, *N*-(2-allylphenyl) cinnamamide (**1g**) efficaciously converted into its corresponding pyrroloindole **2g** in (*Z*)-configuration as evidenced by NOESY in good yield and enantioselectivity (entry 7). Likewise, (*E*)-*N*-(2-allylphenyl)-3-(2-chlorophenyl)acrylamide (**1h**) and (*E*)-*N*-(2-allylphenyl)-3-(4-fluorophenyl)acrylamide (**1i**) also smoothly delivered their corresponding pyrroloindoles **2h** and **2i**, respectively, both in (*Z*)-configurations akin to **2g** as evidenced by NOESY in good yields and comparable enantioselectivities (entries 8 and 9). At the same time, substrates with branched alkene (**1j**) and extended methylene (**1k**) did not react at all under identical model conditions and it is important to note that most of the starting materials (~90%) were recovered in those cases.

**Table 4**
Scope of the Pd(II)-(*M*,*S*,*S*)-*i*-Pr-SPRIX catalyzed reaction [a]

| | | | Yield[b](%) | ee[c](%) |
|---|---|---|---|---|
| |  1a-1d |  2a-2d | | |
| 1 | **1a**: R=Ph | **2a** | 76 | 60 |
| 2 | **1b**: R=Me | **2b** | 73 | 32 |
| 3 | **1c**: R=$-C_4H_8-$ | **2c** | 69 | 27 |
| 4 | **1d**: R=$-C_5H_{10}-$ | **2d** | 82 | 28 |
| |  1e, 1f |  2e, 2f | | |
| 5 | **1e**: R=Ph | **2e** | — | — |
| 6 | **1f**: R=2-Cl–$C_6H_4$ | **2f** | — | — |
| |  1g-1i |  2g-2i | | |
| 7 | **1g**: R=Ph | **2g**[d] | 71 | 54 |
| 8 | **1h**: R=2-Cl–$C_6H_4$ | **2h**[d] | 79 | 61 |
| 9 | **1i**: R=4-F–$C_6H_4$ | **2i**[d] | 63 | 59 |
| |  1j |  2j | | |
| 10 | **1j** | **2j** | — | — |
| |  1k |  2k | | |
| 11 | **1k** | **2k** | — | — |

[a] Reaction conditions: $Pd(TFA)_2$ (10 mol %), (*M*,*S*,*S*)-*i*-Pr-SPRIX (15 mol %), MS 3 Å (25 mg/0.05 mmol substrate), toluene (0.5 mL), $O_2$ (1 atm), 70 °C, 120 h.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] (*Z*)-Configurations were confirmed by NOESY.

A plausible mechanism, as depicted in Scheme 2, consists of an initial step of a coordination between in situ generated Pd(II) complex and an alkene as shown in intermediate **I**. Nucleophilic attack of amine on internal carbon of the olefin in an intramolecular fashion provides the cyclized intermediate **II** via 5-*exo-trig* mode of cyclization (C–N bond formation). Subsequent coordination of the Pd(II) species, thus generated within the intermediate **II**, to the olefin of α,β-unsaturated carbonyl moiety followed by further intramolecular cyclization (C–C bond formation) through similar 5-*exo-trig* mode gives intermediate **III**, which then emancipates the target pyrrolizine **IV** and Pd(II) species **V** after β-hydride elimination. Reoxidation of Pd(0) species, liberated from **V** eventually regenerates the active Pd(II) species with the utilization of molecular oxygen and HX.



**Scheme 2.** A plausible mechanism.

In conclusion, (*M*,*S*,*S*)-*i*-Pr-SPRIX has efficiently been utilized in the Pd(II) catalysis employing molecular oxygen as the sole oxidant. The developed catalytic system manifested its own reactivity on the enantioselective construction of pyrrolizines/pyrroloindoles, imperative scaffolds of bio-important molecules via intramolecular C–N and C–C bond forming reactions with good yields and appreciable enantioselectivities. Efficacious utility of this catalytic system for further development of aerobic asymmetric processes is currently ongoing in our laboratory and will be reported in due course.

## 3. Experimental

### 3.1. General

All the reported melting points were measured in open capillaries with a Laboratory Devices-Mel-Temp II apparatus and are uncorrected. All the reagents are reagent grade and were used without further purification. All solvents used herein were either freshly distilled prior to use or received as anhydrous and were used without further distillation. Thin Layer Chromatography (TLC) was performed on a Silica gel 60 $F_{254}$ plates eluting with the solvents indicated. Column Chromatography was performed on Silica gel (spherical, 63–200 μm) slurry packed in glass columns with eluent system as indicated. All NMR spectra were acquired on a JEOL JNM-LA400 spectrometer at 25 °C using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard ($^{1}$H NMR—400 MHz and $^{13}$C NMR—100 MHz). In the $^{1}$H NMR, chemical shifts are reported in $\delta$ parts per million with reference to TMS and the multiplicities br s, s, d, dd, t, ddt, and m stand for broad singlet, singlet, doublet, doublet of doublet, triplet, double doublet of triplet, and multiplet, respectively. In the $^{13}$C NMR, chemical shifts are reported in $\delta$ ppm with relative to $CDCl_3$. ESI mass spectra were recorded on a Thermo Fisher, LTQ ORBITRAP XL. IR spectra were recorded on a JASCO FT/IR-4100 instrument. HPLC analyses were performed on JASCO HPLC system (JASCO PU 2080 pump and MD-2010 UV/Vis detector). (*M*,*S*,*S*)-*i*-Pr-SPRIX was synthesized by adopting our own method.[4] The precursors of the substrate (**1**), allyl amines were synthesized according to the literature procedures.[3e,15,16]

### 3.2. General procedure for the synthesis of substrates (1)

In a dried RB flask, were taken allyl amine (5.0 mmol) in dichloromethane (20 mL). Pyridine (5.5 mmol) was then added and the mixture was cooled to 0 °C while stirring. Then a solution of acryloyl chloride (5.5 mmol) in dichloromethane (10 mL) was added to the cooled mixture in a drop-wise fashion and allowed to warm to the room temperature. The stirring was continued for over night and the organic layer was separated after quenching with saturated ammonium chloride (30 mL) and the aqueous layer was extracted thrice with dichloromethane (20 mL×3). The combined organic layers, after dried over magnesium sulfate were filtered and concentrated. The residue thus obtained was subjected to silica gel column chromatography (30% ethyl acetate in *n*-hexane) to furnish **1**.

*3.2.1. N-(2,2-Diphenylpent-4-enyl)acrylamide (**1a**).* 2,2-Diphenylpent-4-en-1-amine (1.19 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and acryloyl chloride (0.45 mL, 5.5 mmol) in dichloromethane (30 mL) afforded *N*-(2,2-diphenylpent-4-enyl) acrylamide as a white solid (1.08 g, 74%). Mp 122–123 °C; IR (neat) $\nu$ 3271, 2954, 2338, 1648, 1611, 1533, 1403, 1233 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34–7.30 (m, 4H), 7.26–7.19 (m, 6H), 6.16 (dd, *J*=16.9 Hz; 1.2 Hz, 1H), 5.90 (dd, *J*=16.9 Hz; 10.4 Hz, 1H), 5.56 (dd, *J*=10.4 Hz; 1.2 Hz, 1H), 5.50–5.39 (m, 1H), 5.07 (br.s, 1H), 4.98 (dd, *J*=13.8 Hz; 1.9 Hz, 2H), 4.05 (d, *J*=5.8 Hz, 2H), 2.86 (d, *J*=7.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.4, 145.3, 133.7, 131.0, 128.5, 128.1, 126.7, 126.4, 118.9, 50.4, 46.0, 42.1; HRMS (ESI) calcd for $C_{40}H_{42}N_2NaO_2$: *m*/*z* 605.3144 ([2M+Na]$^+$), found: *m*/*z* 605.3148.

*3.2.2. N-(2,2-Dimethylpent-4-enyl)acrylamide (**1b**).* 2,2-Dimethylpent-4-en-1-amine (0.57 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and acryloyl chloride (0.45 mL, 5.5 mmol) in dichloromethane (30 mL) produced *N*-(2,2-dimethylpent-4-enyl)acrylamide as a white solid (0.56 g, 67%). Mp 108–109 °C; IR (neat) $\nu$ 3297, 2919, 2360, 1658, 1625, 1554, 1408, 1237 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.21 (dd, *J*=16.9 Hz; 1.8 Hz, 1H), 6.07 (dd, *J*=16.9 Hz; 10.1 Hz, 1H), 5.82–5.72 (m, 2H; NH peak is merged), 5.57 (dd, *J*=10.1 Hz; 1.8 Hz, 1H), 5.01–4.95 (m, 2H), 3.12 (d, *J*=6.4 Hz, 2H), 1.93 (d, *J*=7.8 Hz, 2H), 0.84 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.8, 134.9, 131.1, 126.4, 117.6, 49.1, 44.7, 34.9, 25.0; HRMS (ESI) calcd for $C_{20}H_{34}N_2NaO_2$: *m*/*z* 357.2518 ([2M+Na]$^+$), found: *m*/*z* 357. 2525.

*3.2.3. N-[(1-Allylcyclopentyl)methyl]acrylamide (**1c**).* (1-Allylcyclopentyl)methanamine (0.70 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and acryloyl chloride (0.45 mL, 5.5 mmol) in dichloromethane (30 mL) gave *N*-[(1-allylcyclopentyl)methyl]acrylamide as a white solid (0.57 g, 59%). Mp 112–113 °C; IR (neat) $\nu$ 3287, 2951, 2359, 1657, 1625, 1554, 1408, 1237 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.20 (dd, *J*=16.9 Hz; 1.8 Hz, 1H), 6.06 (dd, *J*=16.9 Hz; 10.1 Hz, 1H), 5.84–5.73 (m, 2H; NH peak is merged), 5.56 (dd, *J*=10.1 Hz; 1.8 Hz, 1H), 5.03–5.01 (m, 1H), 4.99–4.97 (m, 1H), 3.20 (d, *J*=6.4 Hz, 2H), 2.04 (d, *J*=7.3 Hz, 2H), 1.62–1.50 (m, 4H), 1.41–1.35 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.9, 135.8, 131.2, 126.2, 117.4, 46.5, 42.8, 35.3, 24.9; HRMS (ESI) calcd for $C_{24}H_{38}N_2NaO_2$: *m*/*z* 409.2831 ([2M+Na]$^+$), found: *m*/*z* 409.2839.

*3.2.4. N-[(1-Allylcyclohexyl)methyl]acrylamide (**1d**).* (1-Allylcyclohexyl)methanamine (0.77 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and acryloyl chloride (0.45 mL, 5.5 mmol) in dichloromethane (30 mL) afforded *N*-[(1-allylcyclohexyl)methyl]acrylamide as a white solid (0.74 g, 71%). Mp 114–115 °C; IR (neat) $\nu$ 3266, 2924, 2359, 1654, 1620, 1559, 1413, 1241 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.27 (dd, *J*=16.9 Hz; 1.8 Hz, 1H), 6.09 (dd, *J*=16.9 Hz; 10.1 Hz, 1H), 5.93–5.83 (m, 1H), 5.64 (dd, *J*=10.1 Hz; 1.4 Hz, 2H; NH peak is merged), 5.12–5.10 (m, 1H), 5.08–5.06 (m, 1H), 3.28 (d, *J*=6.4 Hz, 2H), 2.08 (d, *J*=7.3 Hz, 2H), 1.57–1.40 (m, 6H), 1.36–1.27 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.7, 135.0, 131.1, 126.3, 117.5, 45.9, 41.3, 37.2, 33.6, 26.2, 21.5; HRMS (ESI) calcd for $C_{26}H_{42}N_2NaO_2$: *m*/*z* 437.3144 ([2M+Na]$^+$), found: *m*/*z* 437.3138.

*3.2.5. N-(2-Allylphenyl)cinnamamide (**1g**).* 2-Allylaniline (0.67 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and cinnamoyl chloride (0.94 g, 5.5 mmol) in dichloromethane (30 mL) gave *N*-(2-allylphenyl)cinnamamide as a white solid (1.00 g, 76%). Mp 127–128 °C; IR (neat) $\nu$ 3264, 2915, 2349, 1655, 1622, 1533, 1452, 1227 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.94 (br.s, 1H), 7.76–7.74 (m, 1H), 7.71 (d, *J*=15.6 Hz, 1H), 7.47 (br.s, 2H), 7.36–7.33 (m, 3H), 7.26–7.22 (m, 1H), 7.17–7.17 (m, 1H), 7.14–7.12 (m, 1H), 6.54 (d, *J*=15.6 Hz, 1H), 6.03–5.93 (m, 1H), 5.18 (d, *J*=10.1Hz, 1H), 5.12 (d, *J*=16.9 Hz, 1H), 3.42 (d, *J*=6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.2, 142.1, 136.3, 136.1, 134.6, 130.2, 129.9, 128.8, 127.9, 127.4, 125.4, 123.9, 121.0, 116.7, 36.8; HRMS (ESI) calcd for $C_{36}H_{34}N_2NaO_2$: *m*/*z* 549.2518 ([2M+Na]$^+$), found: *m*/*z* 549.2526.

*3.2.6. (E)-N-(2-Allylphenyl)-3-(2-chlorophenyl)acrylamide (**1h**).* 2-Allylaniline (0.67 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and 2-chlorocinnamoyl chloride (1.11 g, 5.5 mmol) in dichloromethane (30 mL) produced (*E*)-*N*-(2-allylphenyl)-3-(2-chlorophenyl)acrylamide as a white solid (1.25 g, 84%). Mp 161–162 °C; IR (neat) $\nu$ 3254, 2932, 2373, 1655, 1624, 1535, 1454, 1231 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.08, (d, *J*=16.0 Hz, 1H), 8.06 (br.s, 1H), 7.62–7.52 (m, 2H), 7.45–7.42 (m, 1H), 7.37–7.28 (m, 3H), 7.22–7.13 (m, 2H), 6.49 (d, $J$=16.0 Hz, 1H), 6.08–5.98 (m, 1H), 5.24 (d, $J$=10.1 Hz, 1H), 5.16 (d, $J$=16.9 Hz, 1H), 3.45 (d, $J$=6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.6, 144.4, 137.8, 136.4, 136.2, 135.0, 133.1, 130.8, 130.3, 127.7, 127.6, 127.1, 117.0, 37.1; HRMS (ESI) calcd for $C_{36}H_{32}Cl_2N_2NaO_2$: $m/z$ 617.1739 ([2M+Na]$^+$), found: $m/z$ 617.1743.

*3.2.7. (E)-N-(2-Allylphenyl)-3-(4-fluorophenyl)acrylamide (**1i**).* 2-Allylaniline (0.67 g, 5.0 mmol), pyridine (0.44 mL, 5.5 mmol), and 4-fluorocinnamoyl chloride (1.04 g, 5.5 mmol) in dichloromethane (30 mL) afforded (*E*)-*N*-(2-allylphenyl)-3-(4-fluorophenyl)acrylamide as a white solid (0.99 g, 70%). Mp 156–157 °C; IR (neat) $\nu$ 3257, 2945, 2334, 1652, 1621, 1527, 1448, 1246 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (br.s, 1H), 7.69 (d, $J$=15.6 Hz, 1H), 7.53–7.49 (m, 2H), 7.42–7.38 (m, 1H), 7.31–7.27 (m, 1H), 7.21–7.13 (m, 2H), 7.07 (t, $J$=8.7 Hz, 2H), 6.38 (d, $J$=15.6 Hz, 1H), 6.06–5.96 (m, 1H), 5.22 (d, $J$=9.6 Hz, 1H), 5.13 (d, $J$=16.9 Hz, 1H), 3.43 (d, $J$=6.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.0, 162.5, 141.1, 136.4, 136.2, 130.4, 129.9, 129.8, 127.7, 116.9, 116.2, 116.0, 37.1; HRMS (ESI) calcd for $C_{36}H_{32}F_2N_2NaO_2$: $m/z$ 585.2330 ([2M+Na]$^+$), found: $m/z$ 585.2338.

### 3.3. Catalysis: general procedure for the synthesis of pyrrolizines/pyrroloindoles (2)

Under argon atmosphere, a solution of (*M,S,S*)-*i*-Pr-SPRIX (15 mol %), Pd(TFA)$_2$ (10 mol %), and activated molecular sieves (3 Å; 25 mg) in dry toluene (0.3 mL) was stirred at room temperature for 2 h. Substrate **1** (0.05 mmol) followed by dry toluene (0.2 mL) were then added. The reaction vessel was then connected to oxygen (1 atm) and heated to 70 °C for a total period of 120 h. It was cooled to room temperature and then concentrated after passing through a short pad of silica gel followed by rinsing with ethyl acetate. The crude residue thus obtained was purified by silica gel column chromatography (30% ethyl acetate in *n*-hexane) to afford **2a**.

*3.3.1. 2-Methylene-6,6-diphenyltetrahydro-1H-pyrrolizin-3(2H)-one (**2a**).* *N*-(2,2-Diphenylpent-4-enyl)acrylamide (14.6 mg, 0.05 mmol), Pd(TFA)$_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) afforded 2-methylene-6,6-diphenyltetrahydro-1*H*-pyrrolizin-3(2*H*)-one as a white solid (11.0 mg, 76%). Mp 110–111 °C; IR (neat) $\nu$ 2925, 2345, 1689, 1657, 1495, 1300 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25–7.20 (m, 4H), 7.16–7.11 (m, 6H), 5.89 (t, $J$=2.7 Hz, 1H), 5.23 (t, $J$=2.3 Hz, 1H), 4.23 (d, $J$=12.6 Hz, 1H), 3.89 (d, $J$=12.3 Hz, 1H), 3.86–3.82 (m, 1H), 2.91 (ddt, $J$=15.8 Hz; 7.3 Hz; 1.9 Hz, 1H), 2.54–2.46 (m, 2H), 2.09 (t, $J$=11.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.3, 146.3, 142.8, 128.6, 128.5, 126.9, 126.7, 126.6, 115.8, 57.3, 56.9, 54.1, 45.0, 32.3; HRMS (ESI) calcd for $C_{40}H_{38}N_2NaO_2$: $m/z$ 601.2831 ([2M+Na]$^+$), found: $m/z$ 601.2820; The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:1) mixture as an eluent (flow rate=0.6 mL/min; $\lambda$=213 nm; 49.3 min and 56.7 min; 60% ee); $[\alpha]_{D20}$ −5.6 (*c* 0.1, $CHCl_3$).

*3.3.2. 6,6-Dimethyl-2-methylenetetrahydro-1H-pyrrolizin-3(2H)-one (**2b**).* *N*-(2,2-Dimethylpent-4-enyl)acrylamide (8.4 mg, 0.05 mmol), Pd(TFA)$_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) provided 6,6-dimethyl-2-methylenetetrahydro-1*H*-pyrrolizin-3(2*H*)-one as a white solid (6.1 mg, 73%). Mp 99–100 °C; IR (neat) $\nu$ 2923, 2342, 1687, 1655, 1432, 1236 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.85 (t, $J$=2.8 Hz, 1H), 5.20 (t, $J$=2.3 Hz, 1H), 3.92 (m, 1H), 3.39 (d, $J$=11.9 Hz, 1H), 2.93 (ddt, $J$=16.0 Hz; 7.3 Hz; 2.1 Hz, 1H), 2.89 (d, $J$=11.9 Hz, 1H), 2.43–2.36 (m, 1H), 1.78 (dd, $J$=11.9 Hz; 6.0 Hz, 1H), 1.09 (d, $J$=10.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.6, 142.8, 115.4, 57.6, 55.9, 47.4, 41.6, 32.6, 28.8, 28.3; HRMS (ESI) calcd for $C_{20}H_{30}N_2NaO_2$: $m/z$ 353.2205 ([2M+Na]$^+$), found: $m/z$ 353.2197. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:1) mixture as an eluent (flow rate=0.6 mL/min; $\lambda$=240 nm; 19.3 min and 24.3 min; 32% ee); $[\alpha]_{D20}$ −32.4 (*c* 0.1, $CHCl_3$).

*3.3.3. 6′-Methylenetetrahydrospiro[cyclopentane-1,2′-pyrrolizin]-5′(3′H)-one (**2c**).* *N*-[(1-Allylcyclopentyl)methyl]acrylamide (9.7 mg, 0.05 mmol), Pd(TFA)$_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) gave 6′-methylenetetrahydrospiro[cyclopentane-1,2′-pyrrolizin]-5′(3′*H*)-one as a colorless oil (6.6 mg, 69%). IR (neat) $\nu$ 2950, 2353, 1689, 1657, 1411, 1295 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.85 (t, $J$=2.8 HZ, 1H), 5.20 (t, $J$=2.3 Hz, 1H), 3.90–3.83 (m, 1H), 3.48 (d, $J$=11.9 Hz, 1H), 3.00 (d, $J$=11.9 Hz, 1H), 2.92 (ddt, $J$=16.0 Hz; 7.3 Hz; 2.1 Hz, 1H), 2.44–2.37 (m, 1H), 1.86 (dd, $J$=11.9 Hz; 5.5 Hz, 1H), 1.67–1.47 (m, 8H), 1.26 (dd, $J$=11.9 Hz; 10.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.5, 143.0, 115.3, 58.0, 54.6, 52.7, 45.2, 39.3, 38.7, 32.6, 24.4, 24.3; HRMS (ESI) calcd for $C_{24}H_{34}N_2NaO_2$: $m/z$ 405.2518 ([2M+Na]$^+$), found: $m/z$ 405.2510. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:1) mixture as an eluent (flow rate=0.6 mL/min; $\lambda$=246 nm; 21.9 min and 26.9 min; 27% ee); $[\alpha]_{D20}$ −18.8 (*c* 0.1, $CHCl_3$).

*3.3.4. 6′-Methylenetetrahydrospiro[cyclohexane-1,2′-pyrrolizin]-5′(3′H)-one (**2d**).* *N*-[(1-Allylcyclohexyl)methyl]acrylamide (10.4 mg, 0.05 mmol), Pd(TFA)$_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) afforded 6′-methylenetetrahydrospiro[cyclohexane-1,2′-pyrrolizin]-5′(3′*H*)-one as a colorless oil (8.4 mg, 82%). IR (neat) $\nu$ 2925, 2355, 1687, 1656, 1446, 1295 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.84 (t, $J$=2.8 Hz, 1H), 5.20 (t, $J$=2.1 Hz, 1H), 3.86 (m, 1H), 3.44 (d, $J$=12.4 Hz, 1H), 2.94 (d, $J$=11.9 Hz, 1H), 2.91 (ddt, $J$=16.0 Hz; 7.3 Hz; 2.1 Hz, 1H), 2.41–2.34 (m, 1H), 1.91 (dd, $J$=12.4 Hz; 6.0 Hz, 1H), 1.52–1.45 (m, 2H), 1.42–1.32 (m, 8H), 1.07 (dd, $J$=11.9 Hz; 10.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.2, 143.0, 115.3, 56.9, 53.6, 45.8, 38.5, 36.8, 32.4, 25.8, 25.6, 23.9, 23.2; HRMS (ESI) calcd for $C_{26}H_{38}N_2NaO_2$: $m/z$ 433.2831 ([2M+Na]$^+$), found: $m/z$ 433.2822. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:1) mixture as an eluent (flow rate=0.6 mL/min; $\lambda$=250 nm; 36.0 min and 64.0 min; 28% ee); $[\alpha]_{D20}$ −12.8 (*c* 0.1, $CHCl_3$).

*3.3.5. (Z)-2-Benzylidene-9,9a-dihydro-1H-pyrrolo[1,2-a]indol-3(2H)-one (**2g**).* *N*-(2-Allylphenyl) cinnamamide (13.2 mg, 0.05 mmol), Pd (TFA)$_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) afforded (*Z*)-2-benzylidene-9,9a-dihydro-1*H*-pyrrolo[1,2-*a*]indol-3 (2*H*)-one as a white solid (9.3 mg, 71%). Mp 113–114 °C; IR (neat) $\nu$ 2906, 2360, 1686, 1649, 1481, 1302 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.81 (d, $J$=7.3 Hz, 2H), 7.64 (d, $J$=7.8 Hz, 1H), 7.29 (t, $J$=7.6 Hz, 2H), 7.22 (t, $J$=7.3 Hz, 1H), 7.17–7.13 (m, 2H), 6.98 (dt, $J$=7.3 Hz; 0.9 Hz, 1H), 6.72 (d, $J$=2.3 Hz, 1H), 4.63–4.55 (m, 1H), 3.20–3.11 (m, 2H), 2.94–2.84 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.8, 140.0, 135.3, 134.5, 133.8, 130.4, 128.6, 128.0, 127.8, 125.2, 124.5, 115.1, 59.4, 39.0, 36.4; HRMS (ESI) calcd for $C_{36}H_{30}N_2NaO_2$: $m/z$ 545.2205 ([2M+Na]$^+$), found: $m/z$ 545.2196. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD-H as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:5) mixture as an eluent (flow rate=0.5 mL/min; $\lambda$=312 nm; 40.0 min and 45.3 min; 54% ee); $[\alpha]_{\mathrm{D}20}$ −2.2 (*c* 0.1, $CHCl_3$).

*3.3.6. (Z)-2-(2-Chlorobenzylidene)-9,9a-dihydro-1H-pyrrolo[1,2-a]indol-3(2H)-one (**2h**).* (*E*)-*N*-(2-Allylphenyl)-3-(2-chlorophenyl)acrylamide (14.9 mg, 0.05 mmol), $Pd(TFA)_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) afforded (*Z*)-2-(2-chlorobenzylidene)-9,9a-dihydro-1*H*-pyrrolo[1,2-*a*]indol-3(2*H*)-one as a white solid (11.7 mg, 79%). Mp 139–140 °C; IR (neat) $\nu$ 2911, 2344, 1686, 1649, 1481, 1302 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (dd, *J*=7.3 Hz; 1.8 Hz, 1H), 7.65 (d, *J*=7.8 Hz, 1H), 7.36 (dd, *J*=7.3 Hz; 1.8 Hz, 1H), 7.29–7.25 (m, 2H), 7.24–7.18 (m, 2H), 7.05 (dt, *J*=7.3 Hz; 0.9 Hz, 1H), 7.00 (d, *J*=2.8 Hz, 1H), 4.73–4.64 (m, 1H), 3.32–3.22 (m, 2H), 3.01–2.92 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 163.3, 139.8, 136.2, 133.8, 133.5, 132.5, 132.2, 131.4, 129.6, 129.0, 127.9, 126.0, 125.2, 124.7, 115.2, 59.7, 37.8, 36.2; HRMS (ESI) calcd for $C_{36}H_{28}Cl_2N_2NaO_2$: *m*/*z* 613.1426 ($[2M+Na]^+$), found: *m*/*z* 613.1419. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD-H as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:5) mixture as an eluent (flow rate=0.5 mL/min; $\lambda$=314 nm; 39.8 min and 41.8 min; 61% ee); $[\alpha]_{\mathrm{D}20}$ −5.0 (*c* 0.1, $CHCl_3$).

*3.3.7. (Z)-2-(4-Fluorobenzylidene)-9,9a-dihydro-1H-pyrrolo[1,2-a]indol-3(2H)-one (**2i**).* (*E*)-*N*-(2-Allylphenyl)-3-(4-fluorophenyl)acrylamide (14.1 mg, 0.05 mmol), $Pd(TFA)_2$ (1.7 mg, 0.005 mmol), (*M,S,S*)-*i*-Pr-SPRIX (2.81 mg, 0.0075 mmol), and 3 Å molecular sieves (25 mg) in toluene (0.5 mL) afforded (*Z*)-2-(4-fluorobenzylidene)-9,9a-dihydro-1*H*-pyrrolo[1,2-*a*]indol-3(2*H*)-one as a white solid (8.8 mg, 63%). Mp 134–135 °C; IR (neat) $\nu$ 3073, 2350, 1666, 1635, 1481, 1301 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.84 (dd, *J*=8.7 Hz; 5.5 Hz, 2H), 7.63 (d, *J*=7.8 Hz, 1H), 7.16–7.13 (m, 2H), 7.01–6.94 (m, 3H), 6.66 (d, *J*=2.3 Hz, 1H), 4.63–4.54 (m, 1H), 3.20–3.10 (m, 2H), 2.93–2.83 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 163.7, 161.6, 139.9, 134.1, 133.8, 132.5, 132.4, 130.7, 130.6, 127.8, 125.2, 124.6, 115.1, 115.0, 114.8, 59.6, 38.7, 36.3; HRMS (ESI) calcd for $C_{36}H_{28}F_2N_2NaO_2$: *m*/*z* 581.2017 ($[2M+Na]^+$), found: *m*/*z* 581.2009. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD-H as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:5) mixture as an eluent (flow rate=0.5 mL/min; $\lambda$=311 nm; 32.1 min and 35.7 min; 59% ee); $[\alpha]_{\mathrm{D}20}$ −6.4 (*c* 0.1, $CHCl_3$).

### 3.4. Isomerized product of 2a, 6-methyl-2,2-diphenyl-2,3-dihydro-1*H*-pyrrolizin-5(7*aH*)-one (2a′)

Colorless oil; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.25–7.21 (m, 4H), 7.15–7.09 (m, 6H), 5.62–5.58 (m, 1H), 4.54–4.51 (m, 1H), 4.22 (d, *J*=12.5 Hz, 1H), 3.90 (d, *J*=12.3 Hz, 1H), 2.59–2.53 (m, 1H), 2.32 (s, 3H), 2.15–2.11 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.5, 146.3, 142.1, 134.9, 128.6, 128.5, 127.0, 126.7, 126.5, 57.3, 54.4, 45.0, 44.8, 19.9; HRMS (ESI) calcd for $C_{20}H_{19}NNaO$: *m*/*z* 312.1364 ($[M+Na]^+$), found: *m*/*z* 312.1369. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralcel OD as a chiral stationary phase column with *n*-hexane/*i*-PrOH (100:1) mixture as an eluent (flow rate=0.6 mL/min; $\lambda$=216 nm; 45.2 min and 54.6 min; 43% ee).

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