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STUDY OF NOVEL SYNTHETIC METHODOLOGIES FOR INDOLYL DERIVATIVES AND BETA-FLUOROENALS

Xiaobei Chen

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STUDY OF NOVEL SYNTHETIC
METHODOLOGIES FOR INDOYL
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BETA-FLUOROENALS

by

XIAOBEI CHEN

B.S., Pharmacy, Fudan University, P.R. China, 2002
Ph.D., Chemistry, University of New Mexico, USA, 2015

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

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Chemistry

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STUDY OF NOVEL SYNTHETIC METHODOLOGIES FOR
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Abstract

One of the central goals in modern organic synthesis is to develop efficient synthetic strategies for the preparation and study of complex molecules possessing interesting structural, biological, and physical properties. Toward this end, my Ph. D. work focuses on the development of novel synthetic methodologies for the facile construction of synthetically and biologically significant molecular architectures.

The tert-prenylated indoles and indolines are widely present in a large collection of natural products and biologically active compounds. Although significant efforts have been made on the development of efficient methods to prepare these intriguing molecular architectures, few methods have been explored to introduce the challenging reverse prenyl group (1,1-dimethylallyl) at indolyl C2-position. In this regard, we have uncovered the unprecedented efficient aza-Claisen rearrangement involved the two-step reaction of 3-indolyl bromides with enamines as an effective approach to 2-alkylidene substituted indolines. Furthermore, these versatile products have been explored in a
number of new organic transformations to create new organic molecules. A notable example is that we have discovered a divergent Prins cyclization strategy to form indole fused seven-membered cyclic ethers and indoline fused five-membered tetrahydrofurans, respectively. Importantly, a novel variant of the Prins cyclization involving an unprecedented oxygen-participated rearrangement in the formation of the indoline fused five-membered tetrahydrofurans is realized for the first time. It is found that aliphatic aldehydes favor the classic Prins cyclization in the 7-membered ring formation while aromatic and allylic aldehydes for the new non-classic pathway for the formation of the 5-membered ring. The observed experimental results have also been rationalized by the computational studies.

Fluoroalkene (C=CF) is widely used in organic synthesis and this functionality is often employed as a bioisostere for replacement of the peptide bond in the field of peptide and peptidomimetic chemistry. Given its broad utilities while the lack of general methods to construct the important functionality, we have developed a novel organocatalytic and direct conjugate addition of HF to alkynals catalyzed by a simple secondary amine. The highly stereoselective (Z)-β-fluoroenals are generated. The versatile (Z)-β-fluoroenal adducts serve as versatile building blocks in a variety of new organic transformations, thus generating highly valued, structurally diverse fluorinated compounds.
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1. Aza-Claisen Rearrangement Involved Syntheses of 2-Alkylidene Substituted Indolines

1.1 Introduction

The tert-prenylated indoles and indolines are featured in a large collection of natural products and biologically active compounds, such as fellutanine D (1) and cycloechinulin (2).\(^1\) Although extensive efforts have been made on the development of efficient methods for the preparation of these intriguing molecular architectures, few methods have been explored to introduce the challenging reverse prenyl group (1,1-dimethylallyl) at indolyl C2-position (Figure 1.1.1).\(^2\) Because C2 is less electrophilic than C3 and the reverse prenyl group exhibits more highly steric hinderance. Currently, there are only two popular methods used for the installation of the functionality. Nucleophilic tert-prenylation was developed by Danishefsky and coworkers.\(^3\) In this approach, indoles are treated with tert-BuOCl and freshly prepared prenyl-9-BBN at \(-78\) °C (Scheme 1.1.1). However, the use of low temperature and freshly prepared reagents reduces its experimental convenience. The less used Claisen rearrangement was also reported.\(^4\) The 2-\(\text{tert}\) prenylated indolines are obtained through the Claisen rearrangement from the prenylated indole system. The process suffers from poor regioselectivity of tert-prenylation and prenylation (Scheme 1.1.2). Therefore, a general and practical method to prepare 2-alkylidene substituted indole derivatives that bear a sterically demanding quaternary center, and in particular, a method for 2-\(\text{tert}\)-prenylation of indoles, remains to be developed.
1.2 Research Design

The Claisen and the Cope rearrangements are established as reliable protocols to generate defined configured tertiary and quaternary carbon centers.\(^5\) Compared with the Claisen rearrangement, the aza-Claisen rearrangement requires more drastic conditions because more energy is essential to bring the nitrogen atom in the chair topology of the transition state.\(^6,7\) Recently, it has been reported that the quaternized molecules can
significantly reduce the energy and allow the rearrangement to occur at lower temperatures (Scheme 1.2.1). Therefore, we envisioned that the charge-accelerated aza-Claisen rearrangement could be explored for a new reverse prenylation and serve as a suitable key step in our design and syntheses of 2-alkylidene substituted indolines. The resultant new versatile building blocks, 2-(1’, 1’-dimethyl ethanalyl)indolines, can be potentially explored in the syntheses of 2-tert-prenylated indole derivatives (Scheme 1.2.2).

Scheme 1.2.1 Charge-accelerated aza-Claisen rearrangement

Scheme 1.2.2 Strategy in this work (P = protecting group, X = halide substituent).
1.3 Results and Discussion

We commenced our study by optimizing reaction conditions for the proposed aza-Claisen rearrangement followed by hydrolysis using indolyl chloride (3a) and enamine 4a as the starting materials (Table 1.3.1).

Table 1.3.1: Optimization of reaction conditions for the aza-Claisen rearrangement.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive (2 eq.)</th>
<th>(T_2) (°C)</th>
<th>(t_2) (h)</th>
<th>Yield (%) (for 2 steps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>-</td>
<td>100 (no MW)</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>-</td>
<td>100 (no MW)</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>-</td>
<td>100(^b)</td>
<td>0.8</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>EtOH/H₂O=1:2</td>
<td>-</td>
<td>100(^b)</td>
<td>0.8</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>EtOH/H₂O=2:1</td>
<td>-</td>
<td>100(^b)</td>
<td>0.8</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>EtOH/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>0.8</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>-</td>
<td>100(^b)</td>
<td>0.8</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>EtOH/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>EtOH/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>EtOH/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>2.5</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>DMF/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>1.5</td>
<td>41</td>
</tr>
<tr>
<td>12</td>
<td>CH₃CN/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>1.5</td>
<td>44</td>
</tr>
<tr>
<td>13</td>
<td>(i)PrOH/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
<td>14</td>
<td>(i)BuOH/H₂O=4:1</td>
<td>-</td>
<td>100(^b)</td>
<td>1.5</td>
<td>39</td>
</tr>
<tr>
<td>15</td>
<td>(i)PrOH/H₂O=4:1</td>
<td>PhCOOH</td>
<td>100(^b)</td>
<td>1.5</td>
<td>43</td>
</tr>
<tr>
<td>16</td>
<td>(i)PrOH/H₂O=4:1</td>
<td>Bu₃NBr</td>
<td>100(^b)</td>
<td>1.5</td>
<td>38</td>
</tr>
<tr>
<td>17</td>
<td>(i)PrOH/H₂O=4:1</td>
<td>4Å MS</td>
<td>100(^b)</td>
<td>1.5</td>
<td>40</td>
</tr>
</tbody>
</table>

\(^a\) The reactions were carried out on a 0.05 mmol scale of 3a and monitored by appearance of 6a by TLC and ¹H NMR spectroscopy. \(^b\)100 °C was achieved through 100 W microwave irradiation.
According to the theoretical studies of Jorgensen and Severance,\(^9\) protic solvents, which would have a favorable hydrogen-bonding effect on the rate of pericyclic reactions, were chosen to test the reactions initially. Table 1.3.1 summarizes the results of this study in which various solvents, additives and reaction time were probed. An accelerating effect by microwave irradiation was noticed. Without microwave, long reaction time was needed with lower yield (Table 1.3.1, entry 1. 100 °C, 3 h, 22% yield). Under microwave irradiation, the reaction time was shortened and yield was better (Table 1.3.1, entry 3. 0.8 h, 26% yield). The addition of ethanol in water (EtOH/H\(_2\)O = 1:2) resulted in an improving yield (Table 1.3.1, entry 4, 31% yield). The reaction yield was proportional to the increasing ratio of ethanol in the solvent mixture (Table 1.3.1, entry 4-6). However, in pure ethanol, almost no desired product was formed suggesting the critical role of water in the reaction (Table 1.3.1, entry 7). The reaction time was also investigated (Table 1.3.1, entry 6, 8-10). The suitable reaction time was found to be 1.5 h which enabled the reaction to achieve a yield of 48%. Thereby, 1.5-hour was chosen for further optimization. Among different solvent systems probed (Table 1.3.1, entry 8, 11-14), a combination of isopropanol/water (4:1) showed the best result with 51% yield (Table 1.3.1, entry 13). There was no positive effect observed when various additives were used including acid (Table 1.3.1, entry 15), PTC (Table 1.3.1, entry 16) and 4Å MS (Table 1.3.1, entry 17).

The first step was also optimized with various protecting groups, halide substituents and enamines (Table 1.3.2).
Table 1.3.2: Optimization of reaction conditions for the first step.\(^a\)

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>3</th>
<th>4</th>
<th>T(_1) (°C)</th>
<th>t(_1)</th>
<th>Yield (% for 2 steps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a (X = Cl, P = Ac)</td>
<td>4a (N,N-dimethyl-)</td>
<td>rt</td>
<td>9 h</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>3b (X = Cl, P = Ms)</td>
<td>4a</td>
<td>rt</td>
<td>9 h</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>3c (X = Cl, P = Boc)</td>
<td>4a</td>
<td>rt</td>
<td>9 h</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>3d (X = Cl, P = Tf)</td>
<td>4a</td>
<td>rt</td>
<td>9 h</td>
<td>No desired product</td>
</tr>
<tr>
<td>5</td>
<td>3e (X = Br, P = Ms)</td>
<td>4a</td>
<td>rt</td>
<td>2 h</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>3e</td>
<td>4a</td>
<td>rt</td>
<td>1 h</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>3e</td>
<td>4a</td>
<td>rt</td>
<td>0.5 h</td>
<td>58(^b)</td>
</tr>
<tr>
<td>8</td>
<td>3e</td>
<td>4b (pyrrolidin-1-yl)</td>
<td>rt</td>
<td>0.5 h</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>3e</td>
<td>4b</td>
<td>rt</td>
<td>15 min</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>3e</td>
<td>4b</td>
<td>rt</td>
<td>12 min</td>
<td>77</td>
</tr>
<tr>
<td>11</td>
<td>3e</td>
<td>4b</td>
<td>rt</td>
<td>10 min</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>3e</td>
<td>4b</td>
<td>rt</td>
<td>5 min</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>3e</td>
<td>4b</td>
<td>50</td>
<td>12 min</td>
<td>58</td>
</tr>
<tr>
<td>14</td>
<td>3e</td>
<td>4b</td>
<td>0</td>
<td>12 min</td>
<td>33</td>
</tr>
</tbody>
</table>

\(^a\) The reactions were carried out on a 0.05-mmol scale of 3 and monitored by appearance of 6 by TLC and \(^1\)HNMR spectroscopy. \(^b\) Some of 3e remained unreacted.

The first step starting from bromide 3e (Table 1.3.2, entry 5 to entry 14) is much faster than the corresponding reaction from chloride 3b (Table 1.3.2, entry 2). When Ms protected indole bromide 3e was stirred for 1 hour with enamine 4a, a yield of 67% was obtained (Table 1.3.2, entry 6). The enamine salt 5 is not very stable, so longer reaction time is not beneficial (Table 1.3.2, entry 5). When shortening the reaction time of the first step, the reaction did not go to completion (Table 1.3.2, entry 7). So a more stable cyclic enamine 4b was used to replace 4a (Table 1.3.2, entry 8 to 14). When the first step was
carried out at room temperature for 12 minutes using bromide 3e and enamine 4b, a yield of 77% for this two-step reaction was obtained (Table 1.3.2, entry 10). Longer or shorter reaction time in the first step decreased the total yield (Table 1.3.2, entry 8, 9, 11 and 12). Change of the reaction temperature in the first step reduced the yields dramatically (Table 1.3.2, entry 13 and 14). Therefore, the reaction conditions described in entry 10 is optimal.

Having established the optimal reaction conditions, we probed the scope of the process (Table 1.3.3). A variety of indole bromides, bearing electron-donating or -withdrawing substituents (3e–o), were successfully applied and furnished 2,2-dimethyl ethanal at indolyl C2-position using enamine 4b in good yields.

Table 1.3.3: Substrate scope of indole bromides.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>P</th>
<th>(T_1 ({}^\circ\text{C}))</th>
<th>(t_1) (min)</th>
<th>Yield (%, for two steps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3e</td>
<td>Ms</td>
<td>rt</td>
<td>12</td>
<td>6e 77</td>
</tr>
<tr>
<td>2</td>
<td>3f</td>
<td>Ac</td>
<td>rt</td>
<td>15</td>
<td>6f 37</td>
</tr>
<tr>
<td>3</td>
<td>3g</td>
<td>Ts</td>
<td>rt</td>
<td>20</td>
<td>6g 48</td>
</tr>
<tr>
<td>4</td>
<td>3h</td>
<td>5-CH(_3)</td>
<td>Ms</td>
<td>rt</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>3i</td>
<td>5-OCH(_3)</td>
<td>Ms</td>
<td>rt</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>3j</td>
<td>5-F</td>
<td>Ms</td>
<td>rt</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>3k</td>
<td>5-Cl</td>
<td>Ms</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>3l</td>
<td>5-Br</td>
<td>Ms</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>3m</td>
<td>6-Br</td>
<td>Ms</td>
<td>rt</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>3n</td>
<td>5-NO(_2)</td>
<td>Ms</td>
<td>rt</td>
<td>80</td>
</tr>
</tbody>
</table>
The reactions were carried out on a 0.05-mmol scale of 3 and monitored by appearance of 6 by TLC and $^1$HNMR spectroscopy.

| 11 | 3o | 5-CO$_2$Me | Ms | 50 | 15 | 6o | 85 |

Although the yields of the two-step reactions are high in most cases, we observed a trace amount of compound 7 as a side product. We reasoned that the most probable mechanism for generation of compound 7 was $S_{N2}$ reaction of indole bromide 3e (Scheme 1.3.1).

**Scheme 1.3.1** Proposed mechanisms for generation of 6e and 7.
1.4 Derivatization

The second phase of this work was directed towards exploring the utility of these new building blocks 6. One of our major goals for this work is to introduce a reverse prenyl group at indolyl C2-position. In order to achieve this goal, compound 6e was treated with methyltriphénylphosphonium bromide under typical Wittig reaction conditions, and 2-tert-prenylated indoline 8 was obtained effectively. Moreover, reverse prenyl groups bearing various substituents (9 and 10) can be also introduced successfully to compound 6e with the corresponding Wittig reagents (Scheme 1.4.1).

![Scheme 1.4.1 Wittig reactions of 6e. Reagents and conditions: (i) Ph₃PCH₂Br, n-BuLi, THF, 0 °C - rt; (ii) Ph₃PCH₂PhBr, n-BuLi, THF, 0 °C - rt; (iii) Ph₃PCH₂CH₂Br, n-BuLi, THF, 0 °C – rt.]

Interestingly, indoline-fused sultams (11a and 11b) were generated when compound 6e was treated with lithium hydroxide (Scheme 1.4.2). It is noted that sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties.¹⁰ A number of sultams have been reported that exhibit broad biological properties against a variety of enzymes including COX-2,¹¹ HIV integrase,¹² lipoxygenase,¹³ Calpain I¹⁴ and MMP-2¹⁵. In addition, tricyclic lactam 12 was obtained quantitatively from acetyl protected indoline 6f by treatment with

---

9
potassium carbonate. An intramolecular aldol reaction was proposed for the formation of 11a, 11b and 12 (Scheme 1.4.2). It is noteworthy that stryknin (13), a highly toxic alkaloid used as a pesticide, contains a similar moiety in its structure.

**Scheme 1.4.2** Intramolecular Aldol reactions of 6e and 6f. *Reagents and conditions:* (i) LiOH, i-PrOH, reflux; (ii) K$_2$CO$_3$, MeOH, 50 °C.

Exposure of 3-methyleneindoline 15 in the presence of TiCl$_4$ at room temperature resulted in a high yield of the re-aromatized indole 16 (Scheme 1.4.3). Through intramolecular ene reaction cyclopent[b]indole 17 was generated in a very high yield. Significantly, compound 17 is a precursor of natural product Bruceolline D (19). A two-step deprotection and oxidation procedure was employed to convert 17 into the target 19 (Scheme 1.4.3). The total yield from compound 6e to Bruceolline D (19) was 62%. In addition, Bruceolline E (20) and J (21) can be achieved from Bruceolline D (19) by a protocol reported by Lopchuk and Gribble recently.
Scheme 1.4.3 Syntheses of re-aromatised indole 16 and bruceolline D (19). Reagents and conditions: (i) NaBH₄, MeOH, 0 °C; (ii) Ac₂O, DMAP, CH₂Cl₂, 0 °C; (iii) TiCl₄, CH₂Cl₂, rt; (iv) TiCl₄, CH₂Cl₂, rt; (v) MeONa, MeOH, reflux; (vi) IBX, DMSO, rt.

1.5 Conclusions

In summary, we have developed a novel aza-Claisen rearrangement involved a two-step reaction of indole bromides (3) with enamine (4b) as an effective method for the generation of 2-alkylidene substituted indolines (6). These products can be conveniently elaborated to synthesize new molecules, as demonstrated in the preparation of 2-tert-prenylated indolines, indole fused sultams, indole fused lactams and natural product-bruceolline D.
1.6 Experimental Section

General Information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F$_{254}$ were used for thin-layer chromatography (TLC) analysis. Visualisation was effected with ultraviolet light, potassium permanganate or 2,4-dinitrophenylhydrazine as appropriate. $^1$H, 1D-NOE and $^{13}$CNMR spectra were recorded on a Bruker Avance III 300 unless otherwise stated. CDCl$_3$ ($\delta = 7.26$ and 77.0 for $^1$H and $^{13}$CNMR spectra respectively) and DMSO-d$_6$ ($\delta = 2.50$ and 39.5 for $^1$H and $^{13}$CNMR spectra respectively) were used as references. Data for $^1$H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for $^{13}$C NMR are reported as ppm. Multiplicities of carbons were determined by DEPT and comparison with similar compounds. Mass spectra were recorded using a Waters/Micromass LCT Premier instrument.

1.6.1 Preparation of indolyl chloride substrates

1.6.1.1 Procedures for the preparation of substrates 3a
To a solution of aldehyde 22 (2.90 g, 20 mmol) in MeOH (20 mL) was added NaBH₄ (756 mg, 20 mmol) in some portions slowly within 30 min at 0 °C. The reaction was continued to stir at 0 °C for 30 min. Brine 30 mL was added and extracted with EtOAc for three times. The organic layers were combined and dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude product 23 was pure enough to be used directly in the next step. Yield: 100%. ¹H NMR (300 MHz, CDCl₃): δ 8.14 (br, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.29-7.16 (m, 3H), 4.92 (d, J = 3.9 Hz, 2H).

To a solution of compound 23 (770 mg, 5.2 mmol) and imidazole (885 mg, 13 mmol) in DMF (5 mL) was added TBSCl (1.58 g, 10.4 mmol) in one portion. The reaction was stirred at rt for 30 min before water (30 mL) was added and extracted with EtOAc. The aqueous layer was discarded and the organic layer was washed with brine. The organic
layer was dried over anhydrous \( \text{Na}_2\text{SO}_4 \) and the solvent was removed under reduced pressure. The residue was submitted to chromatography to give the desired product 24 (1.37 g, yield: 100%). \(^1\text{H} \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.99 (br, 1H), 7.67 (d, \( J = 7.8 \) Hz, 1H), 7.36 (d, \( J = 8.1 \) Hz, 1H), 7.23-6.97 (m, 3H), 4.95 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H).

![image](image_url)

**1-(3-(((tert-Butyldimethylsilyl)oxy)methyl)-1H-indol-1-yl)ethanone**

To a solution of compound 24 (1.37 g, 5.2 mmol) and \( \text{Et}_3\text{N} \) (2.1 g, 20.8 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added Ac\(_2\)O (2.12 g, 20.8 mmol). The reaction was refluxed for 15 h. Solvent and excess reactants were removed under reduced pressure. The residue was submitted to chromatography to give the desired product 25 (1.40 g, yield: 89%). \(^1\text{H} \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 8.43 (d, \( J = 8.1 \) Hz, 1H), 7.55 (d, \( J = 7.5 \) Hz, 1H), 7.39-7.26 (m, 3H), 4.89 (s, 2H), 2.62 (s, 3H), 0.95 (s, 9H), 0.14 (s, 6H).

![image](image_url)

**1-(3-(Hydroxymethyl)-1H-indol-1-yl)ethanone**
To a solution of compound 25 (1.4 g, 4.6 mmol) in MeOH (20 mL) was added concentrated hydrochloric acid (1.5 mL). The reaction was stirred at rt for 10 min and NaHCO₃ aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc for three times. The organic layers were combined and dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was washed with EtOAc/hexanes = 1/5 to afford pure product 26 (720 mg, 83% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.43 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.43-7.29 (m, 3H), 4.88 (d, J = 5.4 Hz, 2H), 2.63 (s, 3H), 1.65 (t, J = 5.4 Hz, 1H).

1-(3-(Chloromethyl)-1H-indol-1-yl)ethanone

To a solution of compound 26 (720 mg, 3.8 mmol) and Et₃N (768 mg, 7.6 mmol) in CH₂Cl₂ (25 mL) was added MsCl (545 mg, 4.7 mmol) within 15 min at 0 °C. The reaction was stirred at the same temperature for 5 min before the mixture was submitted to chromatography directly (eluted by hexane/EtOAc = 10/1) to give the desired product 3a (468 mg, yield: 59%). ¹H NMR (300 MHz, CDCl₃): δ 8.43 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.43-7.32 (m, 2H), 4.78 (s, 2H), 2.64 (s, 3H).
1.6.1.2 Procedures for the preparation of substrates 3b

![Chemical Structure](image)

1-(Methylsulfonyl)-1H-indole-3-carbaldehyde

To a solution of aldehyde 22 (1.45 g, 10 mmol) and Et<sub>3</sub>N (4.05 mg, 5.6 mL, 40 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0 °C was added MsCl (2.34 μL, 30 mmol) dropwise. After addition, the reaction was warmed to room temperature and stirred for 30 min at rt. Ice-water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 27 (1.83 g, yield 82%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 10.12 (s, 1H), 8.35 (d, <i>J</i> = 7.5 Hz, 1H), 8.12 (s, 1H), 7.90 (d, <i>J</i> = 7.5 Hz, 1H), 7.48 (m, 2H), 3.29 (s, 3H).
(1-(Methylsulfonyl)-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 91% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.92 (d, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 7.2$ Hz, 1H), 7.45 (s, 1H), 7.35 (m, 2H), 4.88 (m, 2H), 3.10 (s, 3H), 1.63 (t, $J = 5.7$ Hz, 1H).

![3b]

3-(Chloromethyl)-1-(methylsulfonyl)-1H-indole

The title compound was prepared in the same procedure as described above in the preparation of compound 3a in 67% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J = 7.2$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.51 (s, 1H), 7.40 (m, 2H), 4.78 (s, 2H), 3.14 (s, 3H).

1.6.1.3 Procedures for the preparation of substrates 3c
**tert-Butyl 3-(((tert-butyl(dimethyl)silyl)oxy)methyl)-1H-indole-1-carboxylate**

To a solution of compound 24 (261 mg, 1.0 mmol) and DMAP (24 mg, 0.2 mmol) in CH$_3$CN (5 mL) was added (Boc)$_2$O (261 mg, 1.5 mmol). The reaction was stirred at rt for 1.5 h. Water was added and the mixture was extracted with EtOAc for three times. The organic layers were combined, dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography to afford the desired product 29 (375 mg, yield: 100%). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.16 (br, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.55 (s, 1H), 7.34 (t, $J = 7.5$ Hz, 1H), 7.26 (t, $J = 7.5$ Hz, 1H), 4.90 (s, 2H), 1.69 (s, 9H), 0.98 (s, 9H), 0.16 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 149.7, 135.8, 129.3, 124.3, 122.2, 121.0, 119.4, 119.7, 83.3, 58.0, 28.1, 27.4, 25.9, 18.4, -5.3.

**tert-Butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate**

The title compound was prepared in the same procedure as described above in the preparation of compound 26 in 93% yield. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.14 (br, 1H),
7.65 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 4.84 (s, 2H), 1.66 (s, 9H).

**tert-Butyl 3-(chloromethyl)-1H-indole-1-carboxylate**

The title compound was prepared in the same procedure as described above in the preparation of compound 3a in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.15 (d, J = 7.8 Hz, 1H), 7.67 (m, 2H), 7.40-7.28 (m, 2H), 4.79 (s, 2H), 1.67 (s, 9H).

**1.6.1.4 Procedures for the preparation of substrates 3d**

1-((Trifluoromethyl)sulfonyl)-1H-indole-3-carbaldehyde

To a solution of aldehyde 22 (290 mg, 2 mmol), Et$_3$N (810 mg, 1.1 mL, 8 mmol) and DMAP (244 mg, 2 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) at 0 °C was added Tf$_2$O (1 mL,
6 mmol) dropwise. After addition, the reaction was stirred for 30 min at 0 °C. Ice-water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 31 (360 mg, yield 65%). 

\[ {^1}H \text{ NMR (500 MHz, CDCl}_3\): } \delta 10.15 (s, 1H), 8.35 (d, \ J = 8.0 \text{ Hz, } 1H), 8.03 (s, 1H), 7.90 (d, \ J = 7.5 \text{ Hz, } 1H), 7.50 (m, 2H). \]

![Structure of 32](image)

(1-((Trifluoromethyl)sulfonyl)-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 95% yield. 

\[ {^1}H \text{ NMR (300 MHz, CDCl}_3\): } \delta 7.91 (dd, \ J_1 = 7.1 \text{ Hz, } J_2 = 1.7 \text{ Hz, } 1H), 7.70 (m, 1H), 7.46-7.38 (m, 3H), 4.89 (d, \ J = 4.5 \text{ Hz, } 2H), 1.72 (t, \ J = 4.5 \text{ Hz, } 1H). \]

![Structure of 3d](image)

3-(Chloromethyl)-1-((trifluoromethyl)sulfonyl)-1H-indole
The title compound was prepared in the same procedure as described above in the preparation of compound 3a in 73% yield. $^1$H NMR (300 MHz, CDCl3): δ 7.92 (dd, $J_1 = 6.6$ Hz, $J_2 = 2.4$ Hz, 1H), 7.74 (dd, $J_1 = 5.6$ Hz, $J_2 = 2.2$ Hz, 1H), 7.49-7.44 (m, 3H), 4.75 (s, 2H).

1.6.2 Preparation of indolyl bromide substrates

1.6.2.1 Procedures for the preparation of substrates 3e

To a solution of compound 28 (3.05 g, 13.5 mmol) in anhydrous CH$_2$Cl$_2$ (30 mL) was added PBr$_3$ (4.8 g, 1.7 mL, 17.6 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 40 min, and then poured into a mixture of ice and saturated NaHCO$_3$ aqueous solution. The resulting mixture was extracted with EtOAc three times. The combined organic phase was washed with water and brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 3e (3.56 g, yield 91%). $^1$H NMR (300 MHz,
CDCl₃): δ 7.90 (dd, J₁ = 6.9 Hz, J₂ = 1.8 Hz, 1H), 7.77-7.74 (m, 1H), 7.53 (s, 1H), 7.46-7.36 (m, 2H), 4.66 (s, 2H), 3.14 (s, 3H).

1.6.2.2 Procedures for the preparation of substrates 3f

1-(3-(Bromomethyl)-1H-indol-1-yl)ethanone

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 68% yield. ¹H NMR (300 MHz, CDCl₃): δ 8.43 (d, J = 7.8 Hz, 1H), 7.70-7.67 (m, 1H), 7.52 (s, 1H), 7.44-7.33 (m, 2H), 4.68 (s, 2H), 2.64 (s, 3H).

1.6.2.3 Procedures for the preparation of substrates 3g
1-Tosyl-1H-indole-3-carbaldehyde

To a solution of aldehyde 22 (1.45 g, 10 mmol), Et$_3$N (2 g, 2.8 mL, 20 mmol) and DMAP (122 mg, 1 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) at 0 °C was added a solution of TsCl (2.86 g, 15 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) dropwise. After addition, the reaction was warmed to rt and stirred for 3.5 hours. Ice-water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with 1M HCl aqueous solution, water and brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 33 (2.85 g, yield 95%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.09 (s, 1H), 8.24 (dd, $J_1$ = 6.8 Hz, $J_2$ = 1.7 Hz, 1H), 8.23 (s, 1H), 7.94 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 7.85 (d, $J$ = 8.3 Hz, 2H), 7.44-7.33 (m, 2H), 7.29 (d, $J$ = 8.3 Hz, 2H).

![Chemical Structure](image)

(1-Tosyl-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 86% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.99 (d, $J$ = 8.1 Hz, 1H), 7.77 (d, $J$ = 8.3 Hz, 2H), 7.61 (dd, $J_1$ = 7.2 Hz, $J_2$ = 0.6 Hz, 1H), 7.55 (s, 1H), 7.34 (t, $J$ = 7.8 Hz, 1H), 7.28-7.26 (m, 1H), 7.22 (d, $J$ = 8.3 Hz, 2H), 4.82 (d, $J$ = 4.5 Hz, 1H), 2.34 (s, 3H), 1.57 (t, $J$ = 5.3 Hz, 1H).
3-(Bromomethyl)-1-tosyl-1H-indole

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 88% yield. $^1$H NMR (500 MHz, CDCl3): δ 7.96 (d, $J = 8.5$ Hz, 1H), 7.78 (d, $J = 8$ Hz, 2H), 7.65 (d, $J = 5.5$ Hz, 1H), 7.64 (s, 1H), 7.36 (t, $J = 8.5$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.24 (d, $J = 8$ Hz, 2H), 4.63 (s, 2H), 2.35 (s, 3H).

1.6.2.4 Procedures for the preparation of substrates 3h

5-Methyl-1H-indole-3-carbaldehyde
POCl₃ (103 μL, 1.1 mmol) was added dropwise to anhydrous DMF (472 μL) that was maintained at 10-20 °C. The resulting mixture was stirred for 30 min and then chilled to 0 °C. A solution of compound 35 (159 mg, 1 mmol) in anhydrous DMF (285 μL) was added. The ice bath was removed and the solution was warmed to rt. After 2 hours, the reaction mixture was poured into ice, 2M NaOH aqueous solution was added until pH was strongly basic. The off-white precipitate was formed and collected, and dried in vacuo to give the desired product 36 (136 mg, yield 86%). ¹H NMR (300 MHz, CDCl₃): δ 10.04 (s, 1H), 8.71 (br, 1H), 8.13 (d, J = 0.6 Hz, 1H), 7.81 (d, J = 3 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.15 (dd, J₁ = 8.4 Hz, J₂ = 1.5 Hz, 1H), 2.49 (s, 3H).

5-Methyl-1-(methylsulfonyl)-1H-indole-3-carbaldehyde

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 69% yield. ¹H NMR (300 MHz, CDCl₃): δ 10.10 (s, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 3.26 (s, 3H), 2.50 (s, 3H).
(5-Methyl-1-(methylsulfonyl)-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J = 8.7$ Hz, 1H), 7.50 (t, $J = 0.8$ Hz, 1H), 7.39 (s, 1H), 7.22 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.4$ Hz, 1H), 4.85 (dd, $J_1 = 5.6$ Hz, $J_2 = 0.8$ Hz, 2H), 3.07 (s, 3H), 2.48 (s, 3H), 1.64 (t, $J = 5.7$ Hz, 1H).

3-(Bromomethyl)-5-methyl-1-(methylsulfonyl)-1H-indole

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J = 8.4$ Hz, 1H), 7.53 (s, 1H), 7.48 (s, 1H), 7.25 (d, $J = 9.9$ Hz, 1H), 4.64 (s, 2H), 3.11 (s, 3H), 2.50 (s, 3H).

1.6.2.5 Procedures for the preparation of substrates 3i
5-Methoxy-1-(methylsulfonyl)-1H-indole-3-carbaldehyde

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 72% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.09 (s, 1H), 8.06 (s, 1H), 7.81-7.75 (m, 2H), 7.08 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H), 3.91 (s, 3H), 3.26 (s, 3H).

(5-Methoxy-1-(methylsulfonyl)-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 78% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.79 (d, $J = 9.0$ Hz, 1H), 7.39 (s, 1H), 7.14 (d, $J = 2.4$ Hz, 1H), 7.00 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H), 4.84 (d, $J = 5.4$ Hz, 2H), 3.87 (s, 3H), 3.06 (s, 3H), 1.68 (t, $J = 5.4$ Hz, 1H).
3-(Bromomethyl)-5-methoxy-1-(methylsulfonyl)-1H-indole

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 90% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.79 (d, $J = 9.0$ Hz, 1H), 7.49 (s, 1H), 7.15 (d, $J = 2.4$ Hz, 1H), 7.03 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H), 4.64 (s, 2H), 3.90 (s, 3H), 3.11 (s, 3H).

1.6.2.6 Procedures for the preparation of substrates 3j

5-Fluoro-1H-indole-3-carbaldehyde

POCl$_3$ (1 mL, 11 mmol) was added dropwise to anhydrous DMF (5 mL) at 0 °C. The resulting mixture was stirred for 30 min at rt and then chilled to 0 °C. A solution of
compound 42 (1.35 g, 10 mmol) in anhydrous DMF (1.4 mL) was added. The ice bath was removed and the solution was warmed to rt. After 3 hours, the reaction mixture was poured into ice, 6M NaOH aqueous solution was added until pH was strongly basic. The mixture was refluxed overnight and then cool to rt. The yellow precipitate was formed and collected, and dried in vacuo to give the desired product 43 (1.0 g, yield 61%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.95 (s, 1H), 7.93 (dd, $J_1 = 9.3$ Hz, $J_2 = 2.4$ Hz, 1H), 7.84 (s, 1H), 7.34 (dd, $J_1 = 9.0$ Hz, $J_2 = 4.5$ Hz, 1H), 7.02 (td, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H).

![Image of compound 44](image_url)

**5-Fluoro-1-(methylsulfonyl)-1H-indole-3-carbaldehyde**

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 66% yield. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.09 (s, 1H), 8.70 (s, 1H), 7.96-7.86 (m, 2H), 7.39 (td, $J_1 = 9.0$ Hz, $J_2 = 2.6$ Hz, 1H), 3.71 (s, 3H).

![Image of compound 45](image_url)

**(5-Fluoro-1-(methylsulfonyl)-1H-indol-3-yl)methanol**
The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 87\% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.85 (dd, $J_1 = 9.0$ Hz, $J_2 = 4.2$ Hz, 1H), 7.48 (s, 1H), 7.38 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.7$ Hz, 1H), 7.12 (td, $J_1 = 9.0$ Hz, $J_2 = 2.7$ Hz, 1H), 4.84 (dd, $J_1 = 5.6$ Hz, $J_2 = 0.8$ Hz, 2H), 3.10 (s, 3H), 1.68 (t, $J = 5.6$ Hz, 1H).

![Chemical structure of 3j](image)

3-(Bromomethyl)-5-fluoro-1-(methylsulfonyl)-1H-indole

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 91\% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.85 (dd, $J_1 = 9.0$ Hz, $J_2 = 4.5$ Hz, 1H), 7.56 (s, 1H), 7.41 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H), 7.15 (td, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H), 4.61 (s, 2H), 3.15 (s, 3H).

1.6.2.7 Procedures for the preparation of substrates 3k

![Chemical structures of substrates 46, 47, 48, and 3k](image)
5-Chloro-1-(methylsulfonyl)-1H-indole-3-carbaldehyde

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 69% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.09 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.83 (d, $J$ = 8.7 Hz, 1H), 7.45 (d, $J$ = 9.0 Hz, 1H), 3.29 (s, 3H).

![Chemical Structure](image)

(5-Chloro-1-(methylsulfonyl)-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 95% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.84 (d, $J$ = 8.9 Hz, 1H), 7.71 (s, 1H), 7.46 (s, 1H), 7.36 (d, $J$ = 8.9 Hz, 1H), 4.85 (d, $J$ = 5.4 Hz, 2H), 3.11 (s, 3H), 1.68 (t, $J$ = 5.4 Hz, 1H).

![Chemical Structure](image)

3-(Bromomethyl)-5-chloro-1-(methylsulfonyl)-1H-indole
The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 86% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.83 (d, $J = 9.0$ Hz, 1H), 7.73 (s, 1H), 7.55 (s, 1H), 7.39 (d, $J = 9.0$ Hz, 1H), 4.61 (s, 2H), 3.15 (s, 3H).

1.6.2.8 Procedures for the preparation of substrates 3l

![Chemical diagram]

5-Bromo-1-(methylsulfonyl)-1H-indole-3-carbaldehyde

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 64% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.09 (s, 1H), 8.53 (s, 1H), 8.11 (s, 1H), 7.78 (d, $J = 9.0$ Hz, 1H), 7.59 (d, $J = 9.0$ Hz, 1H), 3.29 (s, 3H).

![Chemical diagram]

(5-Bromo-1-(methylsulfonyl)-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 96% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.87 (s, 1H),
7.79 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.45 (s, 1H), 4.85 (d, J = 5.4 Hz, 2H), 3.11 (s, 3H), 1.67 (t, J = 5.4 Hz, 1H).

5-Bromo-3-(bromomethyl)-1-(methylsulfonyl)-1H-indole

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 88% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.88 (dd, $J_1$ = 2.0 Hz, $J_2$ = 0.3 Hz, 1H), 7.78 (dd, $J_1$ = 8.7 Hz, $J_2$ = 0.3 Hz, 1H), 7.53 (s, 1H), 7.52 (dd, $J_1$ = 8.7 Hz, $J_2$ = 2.0 Hz, 1H), 4.60 (d, $J$ = 0.9 Hz, 2H), 3.15 (s, 3H).

1.6.2.9 Procedures for the preparation of substrates 3m

6-Bromo-1-(methylsulfonyl)-1H-indole-3-carbaldehyde
The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.10 (s, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 8.09 (s, 2H), 7.58 (d, $J = 8.4$ Hz, 1H), 3.31 (s, 3H).

![Chemical structure](image)

**(6-Bromo-1-(methylsulfonyl)-1H-indol-3-yl)methanol**

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 96% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.10 (d, $J = 1.5$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.46 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz, 1H), 7.42 (s, 1H), 4.86 (d, $J = 5.4$ Hz, 2H), 3.13 (s, 3H), 1.64 (t, $J = 5.4$ Hz, 1H).

![Chemical structure](image)

**6-Bromo-3-(bromomethyl)-1-(methylsulfonyl)-1H-indole**

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.09 (d, $J = 1.5$ Hz, 1H), 7.46 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz, 1H), 6.86 (s, 1H), 4.86 (d, $J = 5.4$ Hz, 2H), 3.13 (s, 3H), 1.64 (t, $J = 5.4$ Hz, 1H).
Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.51 (dd, J₁ = 8.4 Hz, J₂ = 1.8 Hz, 1H), 7.50 (s, 1H), 4.62 (d, J = 0.6 Hz, 2H), 3.17 (s, 3H).

### 1.6.2.10 Procedures for the preparation of substrates 3n

1.6.2.10 Procedures for the preparation of substrates 3n

![Diagram of the synthesis of 5-Nitro-1H-indole-3-carbaldehyde](image)

### 5-Nitro-1H-indole-3-carbaldehyde

The title compound was prepared in the same procedure as described above in the preparation of compound 43 in 80% yield. \(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 10.03 (s, 1H), 8.95 (d, J = 2.1 Hz, 1H), 8.58 (s, 1H), 8.16 (dd, J₁ = 9.0 Hz, J₂ = 2.1 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H).
1-(Methylsulfonyl)-5-nitro-1H-indole-3-carbaldehyde

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 75% yield. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.16 (s, 1H), 8.98 (d, $J = 2.1$ Hz, 1H), 8.90 (s, 1H), 8.38 (dd, $J_1 = 9.3$ Hz, $J_2 = 2.1$ Hz, 1H), 8.15 (d, $J = 9.3$ Hz, 1H), 3.82 (s, 3H).

![Structure 58](image)

(1-(Methylsulfonyl)-5-nitro-1H-indol-3-yl)methanol

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 95% yield. $^1$H NMR (300 MHz, CDCl$_3$ + 2 drops of MeOD-d4): $\delta$ 8.63 (d, $J = 2.1$ Hz, 1H), 8.26 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.1$ Hz, 1H), 7.99 (d, $J = 9.0$ Hz, 1H), 7.59 (s, 1H), 4.87 (s, 2H), 3.19 (s, 3H), 1.78 (s, 1H).

![Structure 3n](image)

3-(Bromomethyl)-1-(methylsulfonyl)-5-nitro-1H-indole
The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 85% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.68 (d, $J = 2.1$ Hz, 1H), 8.33 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.1$ Hz, 1H), 8.03 (d, $J = 9.0$ Hz, 1H), 7.70 (s, 1H), 4.67 (s, 2H), 3.25 (s, 3H).

1.6.2.11 Procedures for the preparation of substrates 3o

![Chemical Structures]

Methyl 3-formyl-1H-indole-5-carboxylate

The title compound was prepared in the same procedure as described above in the preparation of compound 43 in 93% yield. $^1$H NMR (300 MHz, CDCl$_3$ + 2 drops of MeOD-$d_4$): $\delta$ 10.00 (s, 1H), 8.95 (s, 1H), 7.97 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.5$ Hz, 1H), 7.89 (s, 1H), 7.43 (d, $J = 8.7$ Hz, 1H), 3.91 (s, 3H).
Methyl 3-formyl-1-(methylsulfonyl)-1H-indole-5-carboxylate

The title compound was prepared in the same procedure as described above in the preparation of compound 27 in 94% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 10.14 (s, 1H), 9.03 (s, 1H), 8.19 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.8$ Hz, 1H), 8.18 (s, 1H), 7.95 (d, $J = 8.7$ Hz, 1H), 3.98 (s, 3H), 3.33 (s, 3H).

Methyl 3-(hydroxymethyl)-1-(methylsulfonyl)-1H-indole-5-carboxylate

The title compound was prepared in the same procedure as described above in the preparation of compound 23 in 75% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.43 (s, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 7.94 (d, $J = 8.7$ Hz, 1H), 7.52 (s, 1H), 4.92 (d, $J = 5.4$ Hz, 2H), 3.96 (s, 3H), 3.15 (s, 3H), 1.77 (t, $J = 5.4$ Hz, 1H).
Methyl 3-(bromomethyl)-1-(methylsulfonyl)-1H-indole-5-carboxylate

The title compound was prepared in the same procedure as described above in the preparation of compound 3e in 100% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.47 (s, 1H), 8.13 (d, $J = 8.7$ Hz, 1H), 7.94 (d, $J = 8.7$ Hz, 1H), 7.60 (s, 1H), 4.67 (s, 2H), 3.98 (s, 3H), 3.20 (s, 3H).

1.6.3 Preparation of enamine substrates

1.6.3.1 Procedures for the preparation of substrates 4a

\[ \text{CHO} \quad + \quad \text{N}^+ \quad \rightarrow \quad \text{N}^- \]

\[ 63 \quad + \quad 64 \quad \rightarrow \quad 4a \]

$N, N, 2$-Trimethylprop-1-en-1-amine (4a)

To a stirred solution of isobutyr aldehyde 63 (7.2 g, 100 mmol) in Et$_2$O (50 mL) was added dimethylamine 64 (40% aq., 13.5 g, 120 mmol) slowly at 0 °C, followed by the addition of anhydrous Na$_2$SO$_4$ (16 g) in one pot. The mixture was stirred vigorously for 20 min. The solution was transformed into another flask, anhydrous Na$_2$SO$_4$ (8 g) was added at 0 °C and the mixture was stirred vigorously for 10 min. Again, the solution was transformed into another flask, anhydrous Na$_2$SO$_4$ (5 g) was added at 0 °C and the mixture was stirred vigorously for 10 min. Then the solution was transformed into another flask, 4Å MS (9 g) was added and the mixture was stirred very slowly at rt for 5
h. Repeating the above operation for three times and the resulting solution was submitted to distillation to give 3.0 g desired enamine product, 30% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.31 (m, 1H), 2.38 (s, 6H), 1.67 (d, $J = 0.9$ Hz, 3H), 1.60 (d, $J = 0.9$ Hz, 3H).

1.6.3.2 Procedures for the preparation of substrates 4b

![Chemical structure of 4b](image)

1-(2-Methylprop-1-en-1-yl)pyrrolidine (4b)

The title compound was prepared in the same procedure as described above in the preparation of compound 4a in 42% yield as a colorless liquid, b.p. 75-76 °C/75 mmHg (92-106 °C/115-118 mmHg$^{18}$). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.60 (t, $J = 1.1$ Hz, 1H), 2.93 (t, $J = 6.6$ Hz, 4H), 1.77 (m, 4H), 1.69 (s, 3H), 1.62 (s, 3H).

1.6.4 Preparation of products 6 through aza-Claisen rearrangement

1.6.4.1 Typical Procedure for preparation of products 6 from indolyl chloride substrates

![Chemical structures of 3a, 4a, 5a, and 6a](image)

To a solution of compound 3a (10.4 mg, 0.05 mmol) in anhydrous CH$_3$CN (0.2 mL) was added enamine 4a (0.25 mmol, 5 eq.). The reaction was stirred at room temperature
for 9 h before solvent and excess enamine 4a were removed under reduced pressure. To
the residue was added i-PrOH (1.2 mL) and H$_2$O (0.3 mL) and the reaction mixture was
put into microwave condition (100 W, 100 °C) for 90 min. The resulting mixture was
added into brine (10 mL) and extracted with EtOAc for 3 times. The organic layers were
combined and dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced
pressure. The residue was submitted to chromatography to give the desired product 6a as
an oil in 51% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 9.62 (s, 1H), 7.45 (d, J = 7.5 Hz, 1H),
7.28 (t, J = 7.2 Hz, 1H), 7.11 (m, 2H), 5.65 (s, 1H), 5.32 (s, 1H), 5.14 (s, 1H), 2.36 (s,
3H), 1.13 (s, 3H), 0.77 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 202.7, 169.0, 143.7, 141.3,
131.9, 129.6, 124.3, 120.8, 116.0, 106.9, 67.4, 51.5, 24.0, 18.2, 15.9. MS (ESI$^+$) m/z
(M+H)$^+$ calcd for C$_{15}$H$_{18}$NO$_2$ 244.1338, found 244.1336.

1.6.4.2 Procedure for preparation of products 6 from indolyl bromide substrates

\[ \begin{array}{ccc}
\text{3e-o, 1eq.} & + & \text{CH$_3$CN} \\
\text{Microwave 100W,} & \quad & \text{Microwave 100W,} \\
\text{t$_1$, 1PrOH/H$_2$O (4:1),} & \quad & \text{t$_1$, 1PrOH/H$_2$O (4:1),} \\
\text{100 °C, 1.5 h} & \quad & \text{100 °C, 1.5 h} \\
\text{4b, 2eq.} & \rightarrow & \text{6e-o} \\
\end{array} \]

**General Procedure:** To a solution of compound 3 (0.05 mmol, 1 eq.) in anhydrous
CH$_3$CN (0.5 mL) was added enamine 4b (0.1 mmol, 2 eq.). The reaction was stirred at
room temperature or 50 °C for the time listed in Table 1.3.3. To the reaction mixture was
added i-PrOH (1.2 mL) and H$_2$O (0.3 mL), and the resulting solution was put into
microwave condition (100 W, 100 °C). After 90 min of microwave irradiation, the
reaction mixture was added into brine (10 mL) and extracted with EtOAc for 3 times. The
organic layers were combined and dried over anhydrous Na$_2$SO$_4$. The solvent was
removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 6.

2-Methyl-2-(3-methylene-1-(methylsulfonyl)indolin-2-yl)propanal

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.61 (s, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 5.66 (s, 1H), 5.17 (s, 1H), 4.95 (s, 1H), 2.62 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 203.8 (CH), 144.1 (C), 142.6 (C), 132.1 (C), 130.5 (CH), 126.3 (CH), 120.8 (CH), 118.6 (CH), 108.1 (CH$_2$), 70.3 (CH), 51.9 (C), 35.2 (CH$_3$), 18.6 (CH$_3$), 17.5 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{18}$NO$_5$S$^+$ 280.1007, found 280.1008.

2-(1-Acetyl-3-methyleneindolin-2-yl)-2-methylpropanal

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.62 (s, 1H), 7.45 (d, $J = 7.5$ Hz, 1H), 7.28 (t, $J = 7.2$ Hz, 1H), 7.11 (m, 2H), 5.65 (s, 1H), 5.32 (s, 1H), 5.14 (s, 1H), 2.36 (s, 3H), 1.13 (s, 3H), 0.77 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 202.7 (CH), 169.0 (C), 143.7 (C), 141.3 (C), 131.9 (C), 129.6 (CH), 124.3 (CH), 120.8 (CH), 116.0 (CH), 106.9 (CH$_2$), 67.4 (CH),
51.5 (C), 24.0 (CH₃), 18.2 (CH₃), 15.9 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₅H₁₈NO₂⁺ 244.1338, found 244.1336.

![Image of 6g](image1)

**2-Methyl-2-(3-methylene-1-tosylindolin-2-yl)propanal**

¹H NMR (300 MHz, CDCl₃): δ 9.65 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.28 (td, J₁ = 8.1 Hz, J₂ = 1.5 Hz, 1H), 7.19 (dd, J₁ = 7.8 Hz, J₂ = 0.8 Hz, 1H), 7.08-7.05 (m, 3H), 5.29 (d, J = 1.5 Hz, 1H), 4.87 (d, J = 1.5 Hz, 1H), 4.86 (d, J = 4.5 Hz, 1H), 2.30 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 204.0 (CH), 144.3 (C), 144.1 (C), 142.5 (C), 133.5 (C), 132.7 (C), 129.9 (CH), 129.4 (CH), 127.5 (CH), 126.0 (CH), 120.4 (CH), 119.4 (CH), 107.2 (CH₂), 70.4 (CH), 51.7 (C), 21.5 (CH₃), 18.8 (CH₃), 17.7 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₂₀H₂₂NO₅S⁺ 356.1320, found 356.1322.

![Image of 6h](image2)

**2-Methyl-2-(5-methyl-3-methylene-1-(methylsulfonyl)indolin-2-yl)propanal**
$^1$H NMR (300 MHz, CDCl$_3$): δ 9.61 (s, 1H), 7.41 (d, $J = 8.3$ Hz, 1H), 7.23 (s, 1H), 7.12 (d, $J = 8.3$ Hz, 1H), 5.62 (d, $J = 1.2$ Hz, 1H), 5.14 (s, 1H), 4.91 (s, 1H), 2.60 (s, 3H), 2.35 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 203.8 (CH), 142.7 (C), 141.9 (C), 136.3 (C), 132.1 (C), 131.4 (CH), 121.2 (CH), 118.5 (CH), 107.7 (CH$_2$), 70.6 (CH), 51.9 (C), 34.8 (CH$_3$), 21.1 (CH$_3$), 18.6 (CH$_3$), 17.5 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{15}$H$_{20}$NO$_3$S$^+$ 294.1164, found 294.1163.

2-(5-Methoxy-3-methylene-1-(methylsulfonyl)indolin-2-yl)-2-methylpropanal

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.60 (s, 1H), 7.44 (d, $J = 8.7$ Hz, 1H), 6.92 (d, $J = 1.8$ Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 1H), 5.63 (d, $J = 1.5$ Hz, 1H), 5.17 (d, $J = 0.9$ Hz, 1H), 4.91 (t, $J = 1.5$ Hz, 1H), 3.82 (s, 3H), 2.59 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 203.8 (CH), 158.5 (C), 142.9 (C), 137.5 (C), 133.4 (C), 119.9 (CH), 116.7 (CH), 108.3 (CH$_2$), 105.3 (CH), 70.8 (CH), 55.7 (CH$_3$), 51.8 (C), 34.6 (CH$_3$), 18.7 (CH$_3$), 17.5 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{15}$H$_{20}$NO$_3$S$^+$ 310.1113, found 356.1109.
2-(5-Fluoro-3-methylene-1-(methylsulfonyl)indolin-2-yl)-2-methylpropanal

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.60 (s, 1H), 7.50 (dd, $J_1$ = 8.7 Hz, $J_2$ = 4.5 Hz, 1H), 7.11 (dd, $J_1$ = 8.0 Hz, $J_2$ = 2.0 Hz, 1H), 7.02 (t, $J$ = 8.7 Hz, 1H), 5.65 (d, $J$ = 0.9 Hz, 1H), 5.24 (s, 1H), 4.97 (t, $J$ = 1.5 Hz, 1H), 2.62 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 203.5 (CH), 161.4 (d, $J$ = 244.8 Hz, C), 142.1 (C), 140.1 (C), 134.1 (C), 120.2 (d, $J$ = 8.6 Hz, CH), 117.5 (d, $J$ = 24.2 Hz, CH), 109.6 (CH$_2$), 107.7 (d, $J$ = 24.3 Hz, CH), 70.7 (CH), 51.9 (C), 34.9 (CH$_3$), 18.7 (CH$_3$), 17.4 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{17}$FNO$_3$S$^+$ 298.0913, found 298.0906.

![Image of molecule](image)

2-(5-Chloro-3-methylene-1-(methylsulfonyl)indolin-2-yl)-2-methylpropanal

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.59 (s, 1H), 7.47 (d, $J$ = 8.4 Hz, 1H), 7.40 (d, $J$ = 2.1 Hz, 1H), 7.27 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.1 Hz, 1H), 5.66 (d, $J$ = 0.9 Hz, 1H), 5.24 (s, 1H), 4.98 (t, $J$ = 1.5 Hz, 1H), 2.64 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 203.4 (CH), 142.6 (C), 141.6 (C), 133.8 (C), 132.1 (C), 130.4 (CH), 121.0 (CH), 119.7 (CH), 109.7 (CH$_2$), 70.5 (CH), 52.0 (C), 35.2 (CH$_3$), 18.7 (CH$_3$), 17.4 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{17}$ClNO$_3$S$^+$ 314.0618, found 314.0611.
2-(5-Bromo-3-methylene-1-(methylsulfonyl)indolin-2-yl)-2-methylpropanal

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.60 (s, 1H), 7.55 (s, 1H), 7.43 (s, 1H), 7.42 (s, 1H), 5.66 (d, $J = 0.9$ Hz, 1H), 5.23 (s, 1H), 4.97 (t, $J = 1.5$ Hz, 1H), 2.64 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 203.4 (CH), 143.1 (C), 141.5 (C), 134.1 (C), 133.3 (CH), 124.0 (CH), 120.1 (CH), 119.6 (C), 109.7 (CH$_2$), 70.4 (CH), 52.0 (C), 35.3 (CH$_3$), 18.7 (CH$_3$), 17.4 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{17}$BrNO$_3$S$^+$ 358.0113, found 358.0114.

2-(6-Bromo-3-methylene-1-(methylsulfonyl)indolin-2-yl)-2-methylpropanal

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.59 (s, 1H), 7.71 (d, $J = 0.9$ Hz, 1H), 7.35-7.28 (m, 2H), 5.65 (d, $J = 0.9$ Hz, 1H), 5.20 (s, 1H), 4.97 (s, 1H), 2.67 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 203.4 (CH), 145.1 (C), 141.6 (C), 131.1 (C), 129.5 (CH), 124.1 (C), 121.9 (CH), 121.7 (CH), 108.9 (CH$_2$), 70.5 (CH), 52.0 (C), 35.5 (CH$_3$), 18.7 (CH$_3$), 17.4 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{17}$BrNO$_3$S$^+$ 358.0113, found 358.0118.
2-Methyl-2-(3-methylene-1-(methylsulfonyl)-5-nitroindolin-2-yl)propanal

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.60 (s, 1H), 8.29 (d, $J = 2.4$ Hz, 1H), 8.22 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 1H), 7.66 (d, $J = 8.7$ Hz, 1H), 5.85 (dd, $J_1 = 1.8$ Hz, $J_1 = 1.2$ Hz, 1H), 5.38 (t, $J = 1.2$ Hz, 1H), 5.15 (t, $J = 1.8$ Hz, 1H), 2.75 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 202.9 (CH), 148.8 (C), 146.0 (C), 140.5 (C), 133.1 (C), 126.1 (CH), 118.0 (CH), 116.6 (CH), 111.6 (CH$_2$), 70.8 (CH), 52.2 (C), 36.6 (CH$_3$), 18.5 (CH$_3$), 17.3 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{17}$N$_2$O$_3$S$^+$ 325.0858, found 325.0864.

Methyl 2-(2-methyl-1-oxopropan-2-yl)-3-methylene-1-(methylsulfonyl)indolin-5-carboxylate

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.61 (s, 1H), 8.12 (d, $J = 1.5$ Hz, 1H), 8.02 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.5$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 5.77 (d, $J = 1.2$ Hz, 1H), 5.26 (s, 1H), 5.05 (s, 1H), 3.93 (s, 3H), 2.68 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz,
CDCl₃): δ 203.4 (CH), 166.1 (C), 147.6 (C), 141.5 (C), 132.3 (C), 132.1 (CH), 128.2 (C), 122.4 (CH), 117.8 (CH), 109.6 (CH₂), 70.6 (CH), 52.4 (CH₃), 52.1 (C), 35.9 (CH₃), 18.5 (CH₃), 17.3 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₆H₂₀NO₅S⁺ 338.1062, found 338.1062.

1.6.5 Preparation of side products 7 through aza-Claisen rearrangement

Method A: To a solution of aldehyde 7 (1 eq.) in MeOH was added NaBH₄ (1 eq.) in some portions slowly within 30 min at 0 °C. The reaction was continued to stir at 0 °C or rt for 30 min. Brine was added and extracted with EtOAc for three times. The organic layers were combined and dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was submitted to chromatography to give the desired product 66.
2,2-Dimethyl-3-(1-(methylsulfonyl)-1H-indol-3-yl)propan-1-ol

The title compound was prepared in the same procedure as described above in the preparation of compound 6e to generate 7e in 9% yield followed by Method A in 100% yield. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.92 (d, $J = 8.0$ Hz, 1H), 7.69 (d, $J = 7.5$ Hz, 1H), 7.39-7.32 (m, 2H), 7.26 (s, 1H), 3.39 (s, 2H), 3.07 (s, 3H), 2.72 (s, 2H), 0.96 (s, 6H).

3-(5-Fluoro-1-(methylsulfonyl)-1H-indol-3-yl)-2,2-dimethylpropanal

The title compound was prepared in the same procedure as described above in the preparation of compound 6j in 7% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.58 (s, 1H), 7.84 (dd, $J_1 = 9.0$ Hz, $J_2 = 4.2$ Hz, 1H), 7.25 (s, 1H), 7.20 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.7$ Hz, 1H), 7.09 (td, $J_1 = 9.0$ Hz, $J_2 = 2.7$ Hz, 1H), 3.05 (s, 3H), 2.85 (d, $J = 0.6$ Hz, 2H), 1.14 (s, 6H). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{17}$FNO$_3$S$^+$ 298.0913, found 298.0919.
3-(5-Bromo-1-(methylsulfonyl)-1H-indol-3-yl)-2,2-dimethylpropan-1-ol

The title compound was prepared in the same procedure as described above in the preparation of compound 6l to generate 7l in 11% yield followed by Method A in 100% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.81 (d, $J = 1.8$ Hz, 1H), 7.77 (d, $J = 8.7$ Hz, 1H), 7.44 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.8$ Hz, 1H), 7.24 (s, 1H), 3.35 (s, 2H), 3.06 (s, 3H), 2.66 (s, 2H), 0.94 (s, 6H).

![Image of 3-(5-Bromo-1-(methylsulfonyl)-1H-indol-3-yl)-2,2-dimethylpropan-1-ol]

2,2-Dimethyl-3-(1-(methylsulfonyl)-5-nitro-1H-indol-3-yl)propan-1-ol

The title compound was prepared in the same procedure as described above in the preparation of compound 6n to generate 7n in 6% yield followed by Method A in 100% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.66 (d, $J = 2.4$ Hz, 1H), 8.25 (dd, $J_1 = 9.3$ Hz, $J_2 = 2.4$ Hz, 1H), 8.00 (d, $J = 9.3$ Hz, 1H), 7.42 (s, 1H), 3.35 (s, 2H), 3.17 (s, 3H), 2.77 (s, 2H), 0.97 (s, 6H). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{19}$N$_2$O$_5$S$^+$ 327.1015, found 327.1012.

![Image of 2,2-Dimethyl-3-(1-(methylsulfonyl)-5-nitro-1H-indol-3-yl)propan-1-ol]
Methyl 3-(3-hydroxy-2,2-dimethylpropyl)-1-(methylsulfonyl)-1H-indole-5-carboxylate

The title compound was prepared in the same procedure as described above in the preparation of compound 6o to generate 7o in 11% yield followed by Method A in 100% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.40 (d, $J = 1.2$ Hz, 1H), 8.05 (dd, $J_1 = 9.0$ Hz, $J_2 = 1.2$ Hz, 1H), 7.93 (d, $J = 9.0$ Hz, 1H), 7.31 (s, 1H), 3.96 (s, 3H), 3.37 (s, 2H), 3.11 (s, 3H), 2.74 (s, 2H), 0.96 (s, 6H). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{16}$H$_{22}$NO$_3$S$^+$ 340.1219, found 340.1220.

1.6.6 Derivatization of compound 6e

1.6.6.1 Procedure for preparation of 2-tert-prenylated indolines through Wittig reactions

2-(2-Methylbut-3-en-2-yl)-3-methylene-1-(methylsulfonyl)indoline
To a stirred suspension of methyltriphenylphosphonium bromide (93 mg, 0.26 mmol) in anhydrous THF (2 mL) at 0 °C was added 1.6M n-BuLi in hexanes (165 μL, 0.26 mmol) dropwise. The reaction mixture was stirred at the same temperature for 30 min with the formation of a bright yellow coloration. A solution of compound 6e (56 mg, 0.2 mmol) in anhydrous THF (1 mL) was added dropwise. After stirring for 1 hour at 0 °C, the reaction mixture was allowed to warm to rt and stirred at rt for 2 hours. Then, the reaction mixture was quenched with saturated NH₄Cl aqueous solution (10 mL) and extracted with EtOAc for three times. The combined organic phase was washed with brine, dried over anhydrous NaSO₄ and filtered. The solvent was removed under reduced pressure. The residue was submitted to chromatography to give the desired product 8 (61 mg, 100% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.51 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.28 (td, J₁ = 8.1 Hz, J₂ = 1.2 Hz, 1H), 7.16 (td, J₁ = 7.5 Hz, J₂ = 0.9 Hz, 1H), 5.75 (dd, J₁ = 17.1 Hz, J₂ = 11.1 Hz, 1H), 5.63 (d, J = 1.8 Hz, 1H), 5.11 (d, J = 1.5 Hz, 1H), 4.98 (d, J = 0.6 Hz, 1H), 4.93 (dd, J₁ = 8.4 Hz, J₂ = 1.2 Hz, 1H), 4.42 (t, J = 1.5 Hz, 1H), 2.56 (s, 3H), 1.14 (s, 3H), 0.93 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 144.4 (C), 143.2 (CH), 142.8 (C), 132.9 (C), 129.9 (CH), 125.9 (CH), 120.6 (CH), 118.7 (CH), 113.4 (CH₂), 107.8 (CH₂), 74.5 (CH), 42.3 (C), 35.0 (CH₃), 24.3 (CH₃), 21.9 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₅H₂₀NO₂S⁺ 278.1215, found 278.1211.

![Image of化合物9](image-url)
2-(2-Methyl-4-phenylbut-3-en-2-yl)-3-methylene-1-(methylsulfonyl)indoline

The title compound was prepared in the same procedure as described above in the preparation of compound 8 in 66% yield as a mixture of E/Z isomers. The E/Z ratio was determined to be 1:1.5 by $^1$H NMR spectroscopy. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J = 8.1$ Hz, 2.5H), 7.43 (d, $J = 7.5$ Hz, 2.5H), 7.36-7.13 (m, 17.5 H), 6.54 (d, $J = 12.6$ Hz, 1.5H, Z-isomer), 6.28 (d, $J = 16.5$ Hz, 1H, E-isomer), 6.07 (d, $J = 16.5$ Hz, 1H, E-isomer), 5.67 (s, 1.5H, Z-isomer), 5.64 (s, 1H, E-isomer), 5.49 (d, $J = 12.6$ Hz, 1.5H, Z-isomer), 5.26 (s, 1.5H, Z-isomer), 5.11 (s, 1H, E-isomer), 4.54 (s, 1.5H, Z-isomer), 4.51 (s, 1H, E-isomer), 2.59 (s, 3H, E-isomer), 2.55 (s, 4.5H, Z-isomer), 1.26 (s, 3H, E-isomer), 1.08 (s, 3H, E-isomer), 1.04 (s, 4.5H, Z-isomer), 0.79 (s, 4.5H, Z-isomer). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 144.5 (C), 144.4 (C), 143.4 (C), 143.0 (C), 138.9 (C), 137.6 (C), 136.7 (CH), 135.5 (CH), 133.0 (C), 132.9 (C), 130.1 (CH), 130.0 (CH), 129.9 (CH), 128.6 (CH), 128.4 (CH), 127.5 (CH), 127.0 (CH), 126.4 (CH), 126.1 (CH), 125.9 (CH), 120.6 (CH), 120.5 (CH), 118.8 (CH), 118.7 (CH), 107.9 (CH$_2$), 107.7 (CH$_2$), 75.0 (CH), 74.6 (CH), 43.7 (C), 41.9 (C), 35.1 (CH$_3$), 35.0 (CH$_3$), 26.0 (CH$_3$), 24.4 (CH$_3$), 22.7 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{21}$H$_{24}$NO$_2$S$^+$ 354.1528, found 354.1531.

\[\text{(Z)-3-Methylene-2-(2-methylpent-3-en-2-yl)-1-(methylsulfonyl)indoline}\]
The title compound was prepared in the same procedure as described above in the preparation of compound 8 in 86% yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.52 (d, $J$ = 7.5 Hz, 1H), 7.42 (d, $J$ = 7.2 Hz, 1H), 7.28 (t, $J$ = 7.2 Hz, 1H), 7.16 (t, $J$ = 7.5 Hz, 1H), 5.60 (d, $J$ = 1.5 Hz, 1H), 5.47-5.38 (m, 1H), 5.23 (s, 1H), 5.19 (dd, $J_1$ = 12.0 Hz, $J_2$ = 1.5 Hz, 1H), 4.62 (s, 1H), 2.57 (s, 3H), 1.76 (dd, $J_1$ = 7.5 Hz, $J_2$ = 1.5 Hz, 3H), 1.31 (s, 3H), 0.95 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.6 (C), 143.6 (C), 135.4 (CH), 133.2 (C), 129.9 (CH), 126.0 (CH), 125.8 (CH), 120.5 (CH), 118.6 (CH), 107.6 (CH$_2$), 73.9 (CH), 42.4 (C), 35.0 (CH$_3$), 26.2 (CH$_3$), 24.4 (CH$_3$), 14.8 (CH$_3$). The geometry of the olefin was confirmed by 1D-NOE spectra (Table 1.6.6.1.1). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{16}$H$_{22}$NO$_2$S$^+$ 292.1371, found 292.1374.

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<th>Irradiated (ppm)</th>
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<tr>
<td>1.76 (dd, 3H)</td>
<td>5.47-5.38 (m, 1H), 4.62 (s, 1H), 1.31 (s, 3H), 0.95 (s, 3H)</td>
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</table>

### 1.6.6.2 Procedure for preparation of indoline-fused sultams

To a solution of compound 6e (14 mg, 0.05 mmol) in i-PrOH (2 mL) was added anhydrous LiOH (1.8 mg, 0.075 mmol). The resulting mixture was refluxed for 2 hours. The reaction was quenched with saturated NH$_4$Cl aqueous solution and extracted with EtOAc for three times. The combined organic phase was washed with water and brine,
dried over anhydrous Na₂SO₄, and filtered. The solvent was removed under reduced pressure. The residue was submitted to chromatography to give compound 11a (8.2 mg, 59% yield) and compound 11b (5.4 mg, 39% yield).

**Compound 11a:** ¹H NMR (300 MHz, CDCl₃): δ 7.58 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.20 (td, J₁ = 7.8 Hz, J₂ = 1.2 Hz, 1H), 6.97 (td, J₁ = 7.5 Hz, J₂ = 0.9 Hz, 1H), 5.66 (d, J = 2.1 Hz, 1H), 5.14 (d, J = 1.8 Hz, 1H), 4.46 (t, J = 2.0 Hz, 1H), 4.20-4.13 (m, 1H), 3.46 (dd, J₁ = 12.9 Hz, J₂ = 4.2 Hz, 1H), 3.20 (dd, J₁ = 12.9 Hz, J₂ = 11.6 Hz, 1H), 2.03 (m, 1H), 1.25 (s, 3H), 0.67 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 144.3 (C), 141.3 (C), 130.3 (CH), 127.9 (C), 122.6 (CH), 120.5 (CH), 112.0 (CH), 106.4 (CH₂), 73.4 (CH), 70.1 (CH), 53.1 (CH₂), 40.9 (C), 20.1 (CH₃), 11.4 (CH₃). MS (ESI⁺) m/z (M+Na)⁺ calcd for C₁₄H₁₅NNaO₃S⁺ 302.0827, found 302.0829. The relative configuration was determined by 1D-NOE spectra (Table 1.6.6.2.1).

<table>
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<td>0.67 (s, 3H)</td>
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</tr>
<tr>
<td>1.25 (s, 3H)</td>
<td>5.14 (d, 1H), 4.46 (t, 1H), 0.67 (s, 3H)</td>
</tr>
</tbody>
</table>

**Compound 11b:** ¹H NMR (300 MHz, CDCl₃): δ 7.58 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.21 (td, J₁ = 8.1 Hz, J₂ = 1.2 Hz, 1H), 6.98 (td, J₁ = 7.5 Hz, J₂ = 0.9 Hz, 1H), 5.63 (d, J = 2.4 Hz, 1H), 5.10 (d, J = 1.8 Hz, 1H), 4.96 (t, J = 1.8 Hz, 1H), 3.93 (dt, J₁ = 10.2 Hz, J₂ = 3.3 Hz, 1H), 3.78 (d, J = 10.2 Hz, 1H), 3.57 (dd, J₁ = 13.8 Hz, J₂ = 3.3 Hz, 1H), 3.38 (dd, J₁ = 14.1 Hz, J₂ = 3.6 Hz, 1H), 1.25 (s, 3H), 0.75 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 144.2 (C), 141.8 (C), 130.3 (CH), 127.9 (C), 122.7 (CH), 120.6 (CH), 112.0 (CH), 105.4 (CH₂), 76.3 (CH), 68.7 (CH), 51.4 (CH₂), 38.9 (C), 21.2 (CH₃),
18.8 (CH₃). MS (ESI⁺) m/z (M+Na)⁺ calcd for C₁₄H₁₇NNaO₃S⁺ 302.0827, found 302.0816. The relative configuration was determined by 1D-NOE spectra (Table 1.6.6.2.2).

<table>
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<th>Irradiated (ppm)</th>
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<td>1.25 (s, 3H)</td>
<td>5.10 (d, 1H), 4.96 (t, 1H), 0.75 (s, 3H)</td>
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</table>

1.6.6.3 Procedure for preparation of indoline-fused lactams

A solution of compound 6f (13 mg, 0.053 mmol) and K₂CO₃ (11 mg, 0.08 mmol) in MeOH (0.5 mL) was stirred at 50 °C for 1 h. Solvent was removed and the residue was submitted to chromatography to give compound 12 (12.5 mg, 100% yield) as a mixture of diastereomers (dr = 3:1). The product was purified by recrystallization to afford compound 12 (5.9 mg, 47% yield) as a mixture of diastereomers (dr = 6:1). ¹H NMR (300 MHz, CDCl₃): δ 8.27 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 5.65 (d, J = 3.0 Hz, 1H), 5.23 (d, J = 2.4 Hz, 1H), 4.42 (t, J = 2.7 Hz, 1H), 3.88 (t, J = 8.1 Hz, 1H), 3.02 (dd, J₁ = 18.3 Hz, J₂ = 7.5 Hz, 1H), 2.51 (dd, J₁ = 18.3 Hz, J₂ = 8.7 Hz, 1H), 1.38 (s, 3H), 0.77 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 167.1 (C), 143.6 (C), 141.7 (C), 130.0 (CH), 129.5 (C), 124.3 (CH), 119.9 (CH), 117.1 (CH), 104.3 (CH₂), 72.9 (CH), 68.7 (CH), 39.8 (C), 39.4 (CH₂), 22.2 (CH₃), 11.8 (CH₃). MS (ESI⁺)
m/z (M+H)+ calcd for C_{15}H_{18}NO_{2}^+ 244.1338, found 244.1338. The relative configuration of the major diastereomer was determined by 1D-NOE spectra (Table 1.6.6.3.1).

<table>
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<th>Irradiated (ppm)</th>
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<tr>
<td>0.77 (s, 3H)</td>
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<td>1.38 (s, 3H)</td>
<td>5.23 (d, 1H), 4.42 (t, 1H), 3.88 (t, 1H), 0.77 (s, 3H)</td>
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</table>

1.6.6.4 Procedure for preparation of re-aromatized indole 16

2-Methyl-2-(3-methylene-1-(methylsulfonyl)indolin-2-yl)propan-1-ol

The title compound was prepared in the same procedure as described above in Method A in 95% yield. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.53 (d, $J = 8.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 8.0$ Hz, 1H), 5.70 (d, $J = 1.5$ Hz, 1H), 5.19 (s, 1H), 4.62 (s, 1H), 3.94 (dd, $J_1 = 11.5$ Hz, $J_2 = 5.5$ Hz, 1H), 3.18 (dd, $J_1 = 11.5$ Hz, $J_2 = 9.5$ Hz, 1H), 3.09 (dd, $J_1 = 9.0$ Hz, $J_2 = 5.5$ Hz, 1H), 2.62 (s, 3H), 1.08 (s, 3H), 0.43 (s, 3H).
2-Methyl-2-(3-methylene-1-(methylsulfonyl)indolin-2-yl)propyl acetate

To a solution of compound 14 (70 mg, 0.25 mmol) in CH$_2$Cl$_2$ (1 mL) was added DMAP (67.5 mg, 0.55 mmol) followed by Ac$_2$O (47.5 μL, 0.5 mmol) at 0 °C. This reaction mixture was stirred for 0.5 h at 0 °C, and then poured into a saturated aqueous solution of NH$_4$Cl, extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na$_2$SO$_4$, filtered. The solvent was removed under reduced pressure. The residue was submitted to chromatography to give compound 15 (80.2 mg, 100% yield). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 1H), 5.69 (s, 1H), 5.14 (s, 1H), 4.63 (s, 1H), 3.95 (dd, $J_1 = 22.7$ Hz, $J_2 = 11.3$ Hz, 2H), 2.56 (s, 3H), 2.05 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H).

2-Methyl-2-(3-methyl-1-(methylsulfonyl)-1H-indol-2-yl)propyl acetate

To a solution of compound 15 (12.6 mg, 0.04 mmol) in anhydrous CH$_2$Cl$_2$ (1 mL) was added 0.1M TiCl$_4$ in anhydrous CH$_2$Cl$_2$ (78 μL, 0.008 mmol) at rt. The reaction was
stirred at rt for 18 h before iced NaHCO₃ aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc, washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 16 (11.3 mg, 90% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.01–7.98 (m, 1H), 7.47–7.44 (m, 1H), 7.34–7.31 (m, 2H), 4.56 (s, 2H), 2.42 (s, 3H), 2.41 (s, 3H), 2.05 (s, 3H), 1.62 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 170.9 (C), 142.4 (C), 139.9 (C), 134.3 (C), 125.8 (C), 125.7 (CH), 124.9 (CH), 118.8 (CH), 117.5 (CH), 71.0 (CH₂), 39.7 (C), 35.3 (CH₃), 28.4 (CH₃), 21.1 (CH₃), 12.5 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₆H₂₂NO₄S⁺ 324.1270, found 324.1267.

1.6.6.5 Procedure for preparation of Bruceolline D

![Chemical structure diagram]

3,3-Dimethyl-4-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[b]indol-2-ol

To a solution of compound 6e (14 mg, 0.05 mmol) in anhydrous CH₂Cl₂ (1 mL) was added 0.1M TiCl₄ in anhydrous CH₂Cl₂ (0.1 mL, 0.01 mmol) at rt. The reaction was stirred at rt for 2 h before iced NaHCO₃ aqueous solution was added to quench the
reaction. The mixture was extracted with EtOAc, washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 17 (13.6 mg, 97% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.00-7.98 (m, 1H), 7.44-7.41 (m, 1H), 7.30-7.27 (m, 2H), 4.41 (t, J = 6.6 Hz, 1H), 3.16 (dd, J₁ = 15.0 Hz, J₂ = 6.6 Hz, 1H), 3.04 (s, 3H), 2.60 (dd, J₁ = 15.0 Hz, J₂ = 6.6 Hz, 1H), 1.52 (s, 3H), 1.37 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 147.4 (C), 139.7 (C), 126.9 (C), 124.2 (CH), 123.8 (CH), 121.6 (C), 119.4 (CH), 114.5 (CH), 85.1 (CH), 46.3 (C), 40.3 (CH₃), 31.4 (CH₂), 25.5 (CH₃), 19.2 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₄H₁₈NO₃S⁺ 280.1007, found 280.1006.

![Image](image.png)

3,3-Dimethyl-1,2,3,4-tetrahydrocyclopenta[b]indol-2-ol

Compound 17 (30 mg, 0.107 mmol) was added to 3M NaOMe in MeOH (1 mL). The resulting mixture was refluxed for 8 hours. Then, the reaction was cooled to rt and poured into ice, extracted with CH₂Cl₂. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was submitted to chromatography to give compound 18 (15.9 mg, 74% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.81 (br, 1H), 7.46-7.43 (m, 1H), 7.35-7.30 (m, 1H), 7.15-7.06 (m, 2H), 4.46 (t, J = 6.3 Hz, 1H), 3.27 (dd, J₁ = 14.4 Hz, J₂ = 6.9 Hz, 1H), 2.67 (dd, J₁ = 14.4 Hz, J₂ = 6.0 Hz, 1H), 1.37 (s, 3H), 1.24 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 148.1 (C),
139.6 (C), 125.0 (C), 120.9 (CH), 119.8 (CH), 118.7 (CH), 111.7 (C), 111.6 (CH), 85.2 (CH), 43.0 (C), 33.2 (CH₂), 25.5 (CH₃), 20.5 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₃H₁₆NO⁺ 202.1232, found 202.1231.

![Bruceolline D (19)](image)

**3,3-Dimethyl-3,4-dihydrocyclopenta[b]indol-2(1H)-one**

To a solution of compound 18 (10 mg, 0.05 mmol) in DMSO (0.25 mL) was added IBX (45%, 62 mg, 0.1 mmol). The reaction mixture was stirred at rt for 1 h, and then poured into ice-water, extracted with EtOAc for three times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was submitted to chromatography to give bruceolline D 19 (9.1 mg, 86% yield). ¹H NMR (300 MHz, CDCl₃): δ 8.07 (br, 1H), 7.52 (dd, J₁ = 8.4 Hz, J₂ = 0.8 Hz, 1H), 7.41 (dd, J₁ = 7.5 Hz, J₂ = 1.5 Hz, 1H), 7.24-7.14 (m, 2H), 3.55 (s, 2H), 1.39 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 219.8 (C), 146.0 (C), 138.3 (C), 124.5 (C), 122.0 (CH), 120.4 (CH), 119.2 (CH), 111.7 (CH), 109.7 (C), 47.2 (C), 37.4 (CH₂), 24.1 (CH₃). Spectral data were in accordance with those in literature. ¹⁷ MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₃H₁₄NO⁺ 200.1075, found 200.1073.
1.7 References


2. Regioselective Construction of Indoline/Indole Fused Five Membered and Seven Membered Cyclic Ethers Involving A Novel Variation of Prins Cyclization

2.1 Introduction

Indole/indoline fused cyclic ethers are featured in a number of natural products and biologically active molecules. For instance, (−)-phalarine (1, Figure 2.1.1), which was isolated from the perennial grass Phalaris coerulescens in 1999,\(^1\) displayed a [4.3.3.0] fused tricyclic core structure including a furanobisindole ring system and has been the long standing focus of extensive synthetic effort.\(^2\) Although the biological properties of (−)-phalarine has not been reported, the unique and complex molecular architecture still warrants medicinal evaluation since many alkaloids isolated from the genus Phalaris have been proven to be poisonous to livestock when the native plant was ingested (e.g., canary grass, P. arundinacea). Compound 2 was shown to possess potent, bladder-selective smooth muscle relaxant properties by activating the large-conductance Ca\(^{2+}\)-activated potassium channel (BKCa) and thus are potentially useful for the treatment of urge urinary incontinence.\(^3\) Angustilodine (3) and alstilobanine E (4) were discovered in the same Malayan plant Alstonia angustiloba.\(^4\) Alstilobanines E (4) was found to possess modest relaxant activity against phenylephrine-induced contractions of thoracic rat aortic rings with endothelium.\(^4^b\) Compound 5 exhibited cytotoxic effect on osteoblast.\(^5\) Compounds 6 and 7 were shown to elicit substantial estrogen agonist activity while compounds 8 and 9 showed moderate estrogen antagonistic character.\(^6\) Our research work geared toward bioactive compound library development.
A general strategy to generate cyclic ethers is to use the Prins cyclization. The Prins cyclization involves a facile coupling of an unsaturated alcohol and an aldehyde promoted by an acid to form both C-O and C-C bonds in a single step. The cyclization is driven through an oxocarbenium ion intermediate (12) that is generated directly from the corresponding unsaturated alcohol and aldehyde (Scheme 2.1.1). In many examples of the Prins cyclization, a homoallylic alcohol (γ,δ-unsaturated alcohol, 10) is employed to generate a tetrahydropyran (THP) ring exclusively. This is attributed to the transition state (TS1) taking a chair form, which is more stable than that (TS2) of a tetrahydrofuran (THF) ring formation (Scheme 2.1.1). Compared with the numerous examples of 6-membered THP formation, only a small number of examples have been reported to form 5-membered THF products (16). When double bond geometry in the homoallylic alcohol (10) is Z, TS2 can be formed in competition with TS1 due to 1,3-diaxial interaction between H and R3 in TS1. As a result, a mixture of tetrahydropyran and tetrahydrofuran is generated. THF products can be formed exclusively when substituents on the
Homoallylic alcohol meet some particular requirements to stabilize the exocyclic carbocation 14 (i.e., \( R^3 = \text{OH, OR, CH}_2\text{SiR}_3, \text{Ar} \) and terminally dialkyl groups). Therefore, the regioselectivity of the ring-size between THP and THF is dependent on the structure of homoallylic alcohol. To the best of our knowledge, no studies have been reported to synthesize respective THPs and THFs from the same homoallylic alcohol precursors.

![Scheme 2.1.1 General mechanism and regioselectivity of Prins cyclization](image)

Compared with six-membered THP rings, seven-membered cyclic ethers are less stable as a result of transannular (Prelog), bond (Baeyer), and torsional (Pitzer) strains. The synthesis of seven-membered cyclic ethers remains a significant challenge, primarily because both entropic and enthalpic barriers hamper cyclization. Although the Prins cyclization is a powerful method for ring formation, the construction of seven-membered cyclic ethers via Prins cyclization remains elusive. So far, only a few examples have been reported, most of which are intramolecular Prins cyclization. The intramolecular Prins cyclization requires preparation of a precursor for the cyclization. For instance, Overman and his coworkers carried out a seminal work based on this indirect cyclization strategy. A Prins cyclization precursor 20 was prepared from a
silyl activated 4-alken-1-ol 17 which allows intramolecular cyclization to happen under the promotion of an excess of BCl₃ (Scheme 2.1.2). Obviously, the precursors are not easily accessible in such methodologies. Direct and simple methodologies to give seven-membered cyclic ethers via intermolecular Prins cyclization are extremely rare.¹⁶ Furman and coworkers incorporated a methylsilane group with 5-alkyn-1-ol (23) to trap the generated oxocarbenium ion (25) in the Prins cyclization giving 2,7-disubstituted-3-vinylidene oxepanes (24, Scheme 2.1.3).¹⁶a But this method is limited in the scope to aryl aldehydes as the reaction partners. The other method have been developed by Padrón and coworkers in 2012.¹⁶b The cis-2,7- disubstituted oxepanes 28 were successfully synthesized via Prins cyclization from unactivated δ, ε-unsaturated alcohols 27 and aldehydes (Scheme 2.1.4). TMSCl were used in the reaction as the chloride source and thus the amount of Lewis acid - iron (III) salts was reduced to a catalytic amount. However, the scope of this method is limited to alkyl aldehydes.

Scheme 2.1.2 Synthesis of (+)-Isolaurepinnacin (22) via intramolecular Prins cyclization¹⁶d
To the best of our knowledge, examples of regioselectivity of ring-size using Prins cyclization from same unsaturated alcohols have not been reported. Herein, we report a divergent Prins cyclization via a classic and an usual procedure to give seven-membered cyclic ethers and five-membered tetrahydrofurans, respectively. Notably, we made an amazing discovery of a novel variation of Prins cyclization, which is involving a novel procedure of oxygen-participated rearrangement. This new Prins cyclization mechanism is different from the previously reported mechanism and is described for the first time. In addition, the regioselectivity of the ring-size is dependent on the aldehydes, not the
unsaturated alcohols as previously reported examples. When alkyl aldehydes are used, the reactions proceed via a classic Prins cyclization mechanism to afford seven-membered cyclic ethers which are not easily synthesized using other methods. However, when aromatic and allylic aldehydes are used, THFs are generated through the unprecedented cyclization procedure involving oxygen-participated rearrangement.

2.2 Results and Discussion

Our initial investigation focused on the model reaction of equal equivalent indoline 31 and benzaldehyde (32) in the presence of various Brønsted acid and Lewis acid (Table 2.2.1).

Table 2.2.1: Exploration of acid promoted Prins cyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>33a : 33b&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2M H&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt; aq.</td>
<td>DCM</td>
<td>rt</td>
<td>1</td>
<td>decomposed</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv. HF-Py</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>rt</td>
<td>3</td>
<td>decomposed</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>100 equiv. AcOH</td>
<td>DCM</td>
<td>rt</td>
<td>48</td>
<td>No rxn</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>100 equiv. TFA</td>
<td>DCM</td>
<td>rt</td>
<td>0.5</td>
<td>0.8 : 1</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>3 equiv. PhCOOH</td>
<td>PhH</td>
<td>80</td>
<td>16</td>
<td>No rxn</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>3 equiv. pTsOH</td>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>60</td>
<td>3</td>
<td>decomposed</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>3 equiv. 10-CSA</td>
<td>PhH</td>
<td>80</td>
<td>20</td>
<td>2 : 1</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>3 equiv. MsOH</td>
<td>DCM</td>
<td>rt</td>
<td>1</td>
<td>1.4 : 1</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>0.3 equiv. BF&lt;sub&gt;3&lt;/sub&gt;-Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>DCM</td>
<td>rt</td>
<td>1</td>
<td>3 : 1</td>
<td>66</td>
</tr>
<tr>
<td>10</td>
<td>0.3 equiv. TMSOTf</td>
<td>DCM</td>
<td>rt</td>
<td>2</td>
<td>4 : 1</td>
<td>25&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>0.3 equiv. FeCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>DCM</td>
<td>rt</td>
<td>0.5</td>
<td>1 : 1.4</td>
<td>56</td>
</tr>
</tbody>
</table>
When treated with inorganic acid like H$_2$SO$_4$, indoline 31 was decomposed while the benzaldehyde (32) was remained unreacted (Table 2.2.1, entry 1). Regular carboxylic acids, such as acetic acid and benzoic acid, are too weak to carry out the reaction (Table 2.2.1, entry 3 and 5). However, two products 33a and 33b were isolated when trifluoroacetic acid was employed with a little excess of 33b (Table 2.2.1, entry 4). Sulfonic acids were also screened (Table 2.2.1, entry 6 to 8). Camphor-10-sulfonic acid gave better ratio (Table 2.2.1, entry 7) and methyl sulfonic acid delivered better yield (Table 2.2.1, entry 8).

Next, we screened some Lewis acids (Table 2.2.1, entries 9 to 12). TMSOTf gave the best selectivity of product 33a (Table 2.2.1, entry 10). But the reaction was not complete. The yield shown in the table is the conversion percentage. 75% of indoline 31 was remained. It indicated that stoichiometric amounts of TMSOTf are necessary. Meanwhile, when using titanium chloride, all the indoline 31 was consumed (Table 2.2.1, entry 12). However the yield was very low (17%). The major product in this reaction is compound 33c. Compound 33c can also be obtained when treating indoline 31 with 1 equiv. of TMSOTf without adding benzaldehyde (32, Scheme 2.2.1). Although the yield was low, TMSOTf delivered the best selectivity for 33a. Therefore this Lewis acid was chosen for further optimization to selectively produce 33a (Table 2.2.2).

<table>
<thead>
<tr>
<th></th>
<th>0.2 equiv. TiCl$_4$</th>
<th>DCM</th>
<th>rt</th>
<th>1 : 4</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>3 equiv. ZnCl$_2$</td>
<td>CHCl$_3$</td>
<td>rt</td>
<td>24</td>
<td>1.4 : 1</td>
</tr>
</tbody>
</table>

*The reactions were carried out on a 0.025-mmol scale of 31 and monitored by appearance of 33a and 33b by TLC and $^1$HNMR spectroscopy. $^a$The ratio of 33a : 33b was determined by $^1$HNMR spectroscopy. $^c$Yields of isolated mixture of 33a and 33b. $^d$Conversion percentage.
The reaction went to completion when using 1 equivalent TMSOTf (Table 2.2.2, entry 1). Increasing amount of TMSOTf and prolonged reaction time facilitated the selectivity of 33a but the yield was decreased a little bit (Table 2.2.2, entry 2). Further increase of TMSOTf was detrimental to the yield (Table 2.2.2, entry 3). The addition of benzoic acid is useless (Table 2.2.2, entry 4). However, the addition of pyridine resulted in a clean reaction based on the crude proton NMR and the yield increased slightly (Table 2.2.2, entry 5). The only side product in this reaction was compound 33c. Further increase of pyridine resulted in improving the total yield of a mixture of 33a and 33b, but the selectivity of 33a was dropped (Table 2.2.2, entry 6). The addition of 1 equivalent of pyridine decreases the acidity in the reaction. Accordingly, the amount of TMSOTf was further increased to compensate for the loss of acidity. As a result, the reaction ended up with excellent selectivity and good yield of 33a (Table 2.2.2, entry 7). Interestingly, when the reaction time was shortened to 10 minutes, the selectivity of 33a decreased greatly while the generation of 33b increased a lot (Table 2.2.2, entry 8). We suspected that 33b was transformed into 33a. To confirm the transformation, isolated 33b was treated under the conditions described in Table 2.2.2, entry 7. The reaction afforded exclusive 33a as the final product. When trace amount of water was added, the yield and the selectivity decreased dramatically (Table 2.2.2, entry 9). It indicated that the reaction should be run under anhydrous conditions. So activated molecular sieves were added resulting in an
excellent yield of 91% (Table 2.2.2, entry 10). When the reaction was carried out in 300 mg-scale, a quantitative yield was obtained.

Table 2.2.2: Optimization of reaction conditions for selective synthesis of 33a.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>TMSOTf Equiv.</th>
<th>Additive</th>
<th>t (h)</th>
<th>33a : 33b$^b$</th>
<th>(33a + 33b) Yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>5 : 1</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>-</td>
<td>16</td>
<td>Only 33a</td>
<td>71$^e$</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>-</td>
<td>16</td>
<td>Only 33a</td>
<td>33$^e$</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0.2 equiv PhCOOH</td>
<td>16</td>
<td>Only 33a</td>
<td>71$^e$</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.2 equiv Py</td>
<td>16</td>
<td>Only 33a</td>
<td>73$^e$</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1 equiv Py</td>
<td>16</td>
<td>5 : 1</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>1 equiv Py</td>
<td>16</td>
<td>Only 33a</td>
<td>83$^e$</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1 equiv Py</td>
<td>10 min</td>
<td>2.2 : 1</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>1 equiv Py + 2 μL H2O</td>
<td>16</td>
<td>5 : 1</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>1 equiv Py + 4Å MS</td>
<td>16</td>
<td>Only 33a</td>
<td>91$^e$</td>
</tr>
</tbody>
</table>

$^a$The reactions were carried out on a 0.025-mmol scale of 31 and monitored by appearance of 33a and 33b by TLC and $^1$HNMR spectroscopy. $^b$The ratio of 33a : 33b was determined by $^1$HNMR spectroscopy. $^c$Yields of isolated mixture of 33a and 33b. $^d$Conversion percentage. $^e$Yields of isolated 33a.

The structure of product 33a was confirmed by X-ray crystallography (Figure 2.2.1). The fused tetrahydrofuran ring is toward inside and thus the hydrogen on C10 and the styryl group on C7 are toward outside. The NOE observed between the hydrogen on C10 and the methyl group on C7 in compound 33c is consistent with the results from X-ray crystallography of 33a. Therefore, the reaction delivered excellent diastereomeric selectivity. The C13=C14 in the styryl group was found to be in the E conformation.
Figure 2.2.1 Crystal structure of 33a and NOE for 33c.

The scope of the reactions was probed accordingly (Table 2.2.3). Various substitution pattern on the benzene ring in benzaldehydes can be tolerated (Table 2.2.3, entry 2 to 4). The reaction worked well with strong electron-donating and weak electron-withdrawing groups (Table 2.2.3, entry 5 and 6). Strong electron-withdrawing substituent, such as CF$_3$, gave a lower yield (Table 2.2.3, entry 7). Compound 33c was the only side product observed in this case. Higher conjugated electrophiles are also favorable substrates for this reaction (Table 2.2.3, entry 8 to 10). When using allylic aldehyde (Table 2.2.3, entry 11), 43b was increased. However, 43a was still the predominant product in the reaction but lost some control ability of $E/Z$ selectivity. When alkyl aldehydes, such as isobutyl aldehyde (Table 2.2.3, entry 12), were employed under the conditions described in Table 2.2.3, a mixture of 44a, 44b and 33c was obtained after 5 minutes ($44a : 44b : 33c = 1 : 2.5 : 4$). Because product 44b was dominately formed over 44a, we assumed that aliphatic aldehydes might be favorable to generate seven-membered cyclic ethers. To verify our assumption, we used isobutyl aldehyde as the model substrate to screen conditions which could lead to generate seven-membered cyclic ethers exclusively (Table 2.2.4).
Table 2.2.3: Reaction scope for selective synthesis of 33a ~ 44a.\(^a\)

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>a : b(^b)</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-</td>
<td>rt</td>
<td>16</td>
<td>Only 33a</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>p-CH(_3)Ph-</td>
<td>rt</td>
<td>16</td>
<td>Only 34a</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>m-CH(_3)Ph-</td>
<td>rt</td>
<td>16</td>
<td>Only 35a</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>o-CH(_3)Ph-</td>
<td>rt</td>
<td>16</td>
<td>Only 36a</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>p-CH(_2)OPh-</td>
<td>rt</td>
<td>2</td>
<td>Only 37a</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>p-BrPh-</td>
<td>rt</td>
<td>16</td>
<td>Only 38a</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>p-CF(_3)Ph-</td>
<td>rt</td>
<td>16</td>
<td>Only 39a</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>PhCH=CH-</td>
<td>0</td>
<td>5 min</td>
<td>Only 40a</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>PhC≡C-</td>
<td>rt</td>
<td>16</td>
<td>Only 41a</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>naphthalen-1-yl</td>
<td>rt</td>
<td>16</td>
<td>Only 42a</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>CH(_3)CH=CH-</td>
<td>0</td>
<td>10 min</td>
<td>43a : 43b = 7 : 1</td>
<td>63(^d)</td>
</tr>
<tr>
<td>12</td>
<td>(CH(_3))(_2)CH-</td>
<td>rt</td>
<td>5 min</td>
<td>44a : 44b = 1 : 2.5</td>
<td>13</td>
</tr>
</tbody>
</table>

\(^a\)The reactions were carried out on a 0.075-mmol scale of 31 and monitored by appearance of 33a ~ 44a by TLC and \(^1\)HNMR spectroscopy. \(^b\)The ratio of a : b was determined by \(^1\)HNMR spectroscopy. \(^c\)Yields of isolated 33a ~ 44a. \(^d\)Yield of EZ mixture with E : Z = 5 : 1.
When treated with Brønsted acids (Table 2.2.4, entry 1 to 4), the selectivity for 44b was not improved. Then, Lewis acids were studied and it was found that the selectivity was improved (Table 2.2.4, entry 5 to 14). Among them, ZnCl₂ delivered the best outcome without generation of compound 33c (Table 2.2.4, entry 6).

Table 2.2.4: Optimization of acids for selective synthesis of 44b.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>(t)</th>
<th>44a : 44b : 33c(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsOH·Py</td>
<td>24 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>3eq. MsOH</td>
<td>5 min</td>
<td>1 : 1.3 : 0</td>
</tr>
<tr>
<td>3</td>
<td>100eq. TFA</td>
<td>24 h</td>
<td>33c is dominant</td>
</tr>
</tbody>
</table>
Next, we continued to optimize the reaction conditions for selective synthesis of 44b (Table 2.2.5). Various solvents and additives were screened (Table 2.2.5, entries 1 to 5). Chloroform was found to be the optimal one. Decrease of temperature to 4 °C slowed down the reaction and increased generation of compound 44a (Table 2.2.5, entry 8). When the amount of aldehyde was decreased to 5 equivalents and zinc chloride to 1.5 equivalents, the reaction still worked well (Table 2.2.5, entry 11). However, when using 0.3 equivalents of zinc chloride, no reaction happened and all the starting material remained (Table 2.2.5, entry 12). And further decrease of aldehyde to 2 equivalents resulted in a low yield due to the increasing generation of compound 33c (Table 2.2.5, entry 13). As a result, the conditions described in Table 2.2.5, entry 11 were found to be optimal.

<table>
<thead>
<tr>
<th></th>
<th>Reaction Conditions</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3eq. Binol-Phosphoric acid</td>
<td>48 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>3eq. BF₃·Et₂O</td>
<td>1 h</td>
<td>1 : 1.7 : 0</td>
</tr>
<tr>
<td>6</td>
<td>3eq. ZnCl₂</td>
<td>24 h</td>
<td>1 : 13 : 0</td>
</tr>
<tr>
<td>7</td>
<td>3eq. FeCl₃</td>
<td>7 h</td>
<td>33c is dominant</td>
</tr>
<tr>
<td>8</td>
<td>3eq. AlCl₃</td>
<td>6 h</td>
<td>Very messy</td>
</tr>
<tr>
<td>9</td>
<td>3eq. CuCl₂</td>
<td>43 h</td>
<td>33c is dominant</td>
</tr>
<tr>
<td>10</td>
<td>3eq. CuBr₂</td>
<td>43 h</td>
<td>messy</td>
</tr>
<tr>
<td>11</td>
<td>3eq. HgCl₂</td>
<td>43 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>3eq. BiCl₃</td>
<td>6 h</td>
<td>1 : 2 : 0</td>
</tr>
<tr>
<td>13</td>
<td>3eq. SnCl₂</td>
<td>43 h</td>
<td>1 : 6 : 0.5</td>
</tr>
<tr>
<td>14</td>
<td>3eq. InCl₃</td>
<td>12 h</td>
<td>1 : 5 : 0.5</td>
</tr>
</tbody>
</table>

* The reactions were carried out on a 0.025-mmol scale of 31 and monitored by appearance of 44a and 44b by TLC and ¹H NMR spectroscopy. The ratio of 44a : 44b : 33c was determined by crude ¹H NMR spectroscopy.
Table 2.2.5: Optimization of reaction conditions for selective synthesis of 44b.\textsuperscript{a}

![Chemical structure of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv of 45</th>
<th>Equiv of ZnCl\textsubscript{2}</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Additive</th>
<th>t (h)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3</td>
<td>CH\textsubscript{3}CN</td>
<td>rt</td>
<td>-</td>
<td>15</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>3</td>
<td>DMSO</td>
<td>rt</td>
<td>-</td>
<td>15</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>3</td>
<td>DMF</td>
<td>rt</td>
<td>-</td>
<td>15</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>3</td>
<td>PhCH\textsubscript{3}</td>
<td>rt</td>
<td>-</td>
<td>16</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>3</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>-</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>3</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>4Å MS powder</td>
<td>27</td>
<td>&lt; 10\textsuperscript{c}</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>3</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>1 equiv py</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>3</td>
<td>CHCl\textsubscript{3}</td>
<td>4</td>
<td>-</td>
<td>72</td>
<td>&lt; 70\textsuperscript{c}</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>3</td>
<td>CHCl\textsubscript{3}</td>
<td>50</td>
<td>-</td>
<td>8</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>3</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>-</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>1.5</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>-</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>0.3</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>-</td>
<td>24</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>1.5</td>
<td>CHCl\textsubscript{3}</td>
<td>rt</td>
<td>-</td>
<td>24</td>
<td>56</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The reactions were carried out on a 0.025-mmol scale of 31 and monitored by appearance of 44b by TLC and \textsuperscript{1}HNMR spectroscopy. \textsuperscript{b}Yields of isolated 44b. \textsuperscript{c}Conversion percentage.

The optimized protocol can be employed for the reactions of a variety of alkyl aldehydes and indoline 31 (Table 2.2.6). The reaction worked well with both linear and branched aliphatic aldehydes (Table 2.2.6, entries 1 to 9). But hydrocinnamaldehyde delivered a lower yield due to the increasing generation of 53a (Table 2.2.6, entry 10). As expected, when using benzaldehyde, the reaction was very messy and 33a was obtained a little more than 33b (Table 2.2.6, entry 11). The total yield of 33a and 33b in this case was less than 30%.
Table 2.2.6: Reaction scope for selective synthesis of 44b ~ 53b.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>44b ~ 53b</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH(_3))_2CH-</td>
<td>44b</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>CH(_3)CH(_2)-</td>
<td>45b</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>CH(_3)(CH(_2))_2CH(_3)-</td>
<td>46b</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>CH(_3)(CH(_2))_2CH(_2)-</td>
<td>47b</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>CH(_3)(CH(_2))_2CH(_3)-</td>
<td>48b</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>(CH(_3))_2CHCH(_2)-</td>
<td>49b</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>CH(_3)CH(_3)(CH(_3))CH-</td>
<td>50b</td>
<td>68(^c)</td>
</tr>
<tr>
<td>8</td>
<td>CH(_3)(CH(_2))_2(CH(_3))CH-</td>
<td>51b</td>
<td>77(^c)</td>
</tr>
<tr>
<td>9</td>
<td>(\text{c-C}<em>6\text{H}</em>{11})-</td>
<td>52b</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>PhCH(_2)CH(_2)-</td>
<td>53b</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>Ph-</td>
<td>33b</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\)The reactions were carried out on a 0.075-mmol scale of 31 and monitored by appearance of 44b ~ 53b by TLC and \(^1\)HNMR spectroscopy. \(^b\)Yields of isolated 44b ~ 53b. \(^c\)Products are diastereomer mixtures.
Because observed 33b could be transformed into 33a (Table 2.2.2, entry 1, 2, 7 and 8), we proposed that the reaction of indoline 31 and an aldehyde generates the oxocarbenium ion 54 which evolves to the corresponding seven-membered cyclic ethers 44b to 53b via the carbocation 55 (Scheme 6). THFs 33a to 43a could be generated from the corresponding bicycle 56 via the carbocation 57 which should be more stable than the carbocation 55 when R is aromatic or allylic substituent. This proposed mechanism explains why 33a to 43a was obtained exclusively when R is aromatic or allylic substituent. It also rationalizes that 39a was obtained in a moderate yield because strong electron-withdrawing substituents on the benzene ring destabilize the carbocation 57. To our knowledge, such Prins cyclization mechanism for the synthesis of 33a to 43a is different from the previously reported mechanism.

Scheme 2.2.2 Proposed mechanism for regioselective synthesis of 33a ~ 43a and 44b ~ 53b

Interestingly, when cyclopropanecarboxaldehyde (58) was used under the classic Prins cyclization conditions, the reaction did not generate seven-membered cyclic ether. Instead, a ring opening product 59 was obtained in a quantitative yield (Scheme 2.2.3).
The chloride may facilitate the ring opening process. The single double bond position was verified by $^1$H-$^1$H COSY.

![Scheme 2.2.3 Proposed mechanism for synthesis of 59]

### 2.3 Computational Study for Mechanistic Investigations

To fully understand the reaction mechanism of the unusual Prins cyclization reaction for the synthesis of 33a to 43a, we employ the DFT (M06$^{17}$/6-31+G*$^{18}$) methods to investigate the electronic structure and energetics along the reaction potential energy surface (PES), where the effect of solvent is considered with the polarizable continuum medium (PCM)$^{19}$ model. To facilitate the calculations, R was designated as ethyl group (alkylic substituent) and phenyl group (aromatic substituent) specifying R/S configuration.

Starting from seven-membered cyclic carbocation 55 (Scheme 2.3.1), in path-$b$-Et pro-products 55b (R = Et) were located through a water-mediated proton-transfer pathway, where the energy barriers are calculated to be 19.2 and 18.9 kcal/mol in $S$ and $R$ chiral structures, respectively (Figure 2.3.1). On the other hand, in path-$a$-Et the cyclic torsion of carbocation 55 could generate bicycle 56 and the corresponding carbocation 57.
through 55a. Carbocation 57-Et is less stable than carbocation 55-Et by ~22 kcal/mol. It is noteworthy that seven-membered cyclic ethers (product b) were slightly favorable compared with THFs (product a) when R is ethyl substituent.

![Scheme 2.3.1 Proposed pathways of carbocation 55](image)

Next, the reaction mechanism with R designated as phenyl group was investigated. Also a water-mediated proton-transfer pathway was found in path-b-Ph, where the energy barriers are 18.9 kcal/mol in both R and S configurations (Figure 2.3.2). Interestingly, different from path-a-Et, the energy barriers of the rate-determine-step in path-a-Ph, which is the formation of carbocation 57, are 12.7 and 10.9 kcal/mol in S and R configurations, respectively. These barriers are much lower than those in path-b-Ph (Figure 2.3.2) and in path-a-Et (Figure 2.3.1). It should be noted that compared with seven-membered cyclic ethers (product b), THFs (product b) are the more favorable products when R is phenyl substituent.
Moreover, the deprotonation of carbocation 57 to generate product a in path-a with a base could proceed through different approaches and reception directions, therefore, four isomers will be obtained including cis-Et, trans-Et, cis-Ph and trans-Ph. According to our calculations the trans-products are much lower in free energy than the cis-products. It is proposed that trans-products have less steric hindrance and more matched electronic orientation between H and the lone pair of the oxygen in THF. In detail, the trans-Et is 3.2 kcal/mol lower in free energy than the cis-Et in gas phase and 2.8 kcal/mol lower in
chloroform, while the *trans-Ph* is 7.9 kcal/mol lower in free energy than the *cis-Ph* in gas phase and 6.4 kcal/mol lower in chloroform. Optimized structures of isomers a with free energies are demonstrated in Figure 2.3.3.

**Figure 2.3.2** Free energy profiles of carbocation 55 with phenyl group
2.4 Conclusions

In summary, we have developed a divergent Prins cyclization via a classic and an unusual processes involving oxygen-participated rearrangement to give seven-membered cyclic ethers and five-membered tetrahydrofurans, respectively. The nature of products formed depends on the aldehyde substrates. Aliphatic aldehydes facilitate the classic Prins cyclization pathway to afford the seven-membered cyclic ethers. However, when aromatic and allylic aldehydes are used, new five-membered tetrahydrofurans are generated through the novel Prins cyclization process. The mechanisms of the Prins cyclizations are rationalized by computational studies.
2.5 Experimental Section

**General Information:** Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F\textsubscript{254} were used for thin-layer chromatography (TLC) analysis. Visualisation was effected with ultraviolet light, potassium permanganate or 2,4-dinitrophenylhydrazine as appropriate. \textsuperscript{1}H, \textsuperscript{1}D-NOE and \textsuperscript{13}CNMR spectra were recorded on a Bruker Avance III 300 unless otherwise stated. CDCl\textsubscript{3} (\(\delta = 7.26\) and 77.0 for \textsuperscript{1}H and \textsuperscript{13}CNMR spectra respectively) and DMSO-d\textsubscript{6} (\(\delta = 2.50\) and 39.5 for \textsuperscript{1}H and \textsuperscript{13}CNMR spectra respectively) were used as references. Data for \textsuperscript{1}H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for \textsuperscript{13}C NMR are reported as ppm. Multiplicities of carbons were determined by DEPT and comparison with similar compounds. Mass spectra were recorded using a Waters/Micromass LCT Premier instrument.

2.5.1 Preparation of indoline substrate 31

![Chemical diagram of indoline substrate preparation](image)

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85
1-(Methylsulfonyl)-1H-indole-3-carbaldehyde

To a solution of aldehyde 63 (1.45 g, 10 mmol) and Et₃N (4.05 mg, 5.6 mL, 40 mmol) in anhydrous CH₂Cl₂ (20 mL) at 0 °C was added MsCl (2.34 μL, 30 mmol) dropwise. After addition, the reaction was warmed to room temperature and stirred for 30 min at rt. Ice-water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 64 (1.83 g, yield 82%). ¹H NMR (500 MHz, CDCl₃): δ 10.12 (s, 1H), 8.35 (d, J = 7.5 Hz, 1H), 8.12 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.48 (m, 2H), 3.29 (s, 3H).

(1-(Methylsulfonyl)-1H-indol-3-yl)methanol

To a solution of aldehyde 64 (2.90 g, 20 mmol) in MeOH (20 mL) was added NaBH₄ (756 mg, 20 mmol) in some portions slowly within 30 min at 0 °C. The reaction was continued to stir at 0 °C for 30 min. Icy water 100 mL was added and a large amount of white precipitate formed. The mixture was filtered to afford pure alcohol 65 in 91% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.92 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.45 (s, 1H), 7.35 (m, 2H), 4.88 (m, 2H), 3.10 (s, 3H), 1.63 (t, J = 5.7 Hz, 1H).
3-(Bromomethyl)-1-(methylsulfonyl)-1H-indole

To a solution of compound 65 (3.05 g, 13.5 mmol) in anhydrous CH$_2$Cl$_2$ (30 mL) was added PBr$_3$ (4.8 g, 1.7 mL, 17.6 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 40 min, and then poured into a mixture of ice and saturated NaHCO$_3$ aqueous solution. The resulting mixture was extracted with EtOAc three times. The combined organic phase was washed with water and brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product 66 (3.56 g, yield 91%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.90 (dd, $J_1$ = 6.9 Hz, $J_2$ = 1.8 Hz, 1H), 7.77-7.74 (m, 1H), 7.53 (s, 1H), 7.46-7.36 (m, 2H), 4.66 (s, 2H), 3.14 (s, 3H).

2-Methyl-2-(3-methylene-1-(methylsulfonyl)indolin-2-yl)propanal

To a solution of compound 66 (144 mg, 0.5 mmol) in anhydrous CH$_3$CN (1.0 mL) was added enamine 67 (125 mg, 1 mmol). The reaction was stirred at room temperature for 12 min. To the reaction mixture was added $i$-PrOH (2.4 mL) and H$_2$O (0.6 mL), and the resulting solution was put into microwave condition (100 W, 100 °C). After 90 min of microwave irradiation, the reaction mixture was added into brine (10 mL) and extracted
with EtOAc for 3 times. The organic layers were combined and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 68 (107 mg, yield 77%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.61 (s, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 5.66 (s, 1H), 5.17 (s, 1H), 4.95 (s, 1H), 2.62 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 203.8 (CH), 144.1 (C), 142.6 (C), 132.1 (C), 130.5 (CH), 126.3 (CH), 120.8 (CH), 118.6 (CH), 108.1 (CH$_2$), 70.3 (CH), 51.9 (C), 35.2 (CH$_3$), 18.6 (CH$_3$), 17.5 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{14}$H$_{18}$NO$_3$S$^+$ 280.1007, found 280.1008.

![Image of compound 31]

2-Methyl-2-(3-methylene-1-(methylsulfonyl)indolin-2-yl)propan-1-ol

To a solution of aldehyde 68 (894 mg, 3.2 mmol) in MeOH was added NaBH$_4$ (121 mg, 3.2 mmol) in some portions slowly within 30 min at 0 °C. The reaction was continued to stir at 0 °C for 30 min. Brine was added and extracted with EtOAc for three times. The organic layers were combined and dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was submitted to chromatography to give the desired product 31 (855 mg, yield 95%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J = 8.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 8.0$ Hz, 1H), 5.70 (d, $J = 1.5$ Hz, 1H), 5.19 (s, 1H), 4.62 (s, 1H), 3.94 (dd, $J_1 = 11.5$ Hz, $J_2 = 5.5$ Hz, 1H), 3.18 (dd, $J_1 = 11.5$ Hz, $J_2 = 9.5$ Hz, 1H), 3.09 (dd, $J_1 = 9.0$ Hz, $J_2 =
5.5 Hz, 1H), 2.62 (s, 3H), 1.08 (s, 3H), 0.43 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 143.8 (C), 142.6 (C), 133.0 (C), 129.9 (CH), 126.2 (CH), 120.4 (CH), 118.8 (CH), 108.1 (CH$_2$), 70.4 (CH), 68.5 (CH$_2$), 40.9 (C), 34.5 (CH$_3$), 20.3 (CH$_3$), 18.2 (CH$_3$).

2.5.2 Preparation of products 33a ~ 43a

![Chemical structure](image)

**General Procedure:** To a solution of compound 31 (21 mg, 0.075 mmol, 1 eq.) in anhydrous CHCl$_3$ (1.5 mL) was added aldehyde (0.075 mmol, 1 eq.), pyridine (6 μL, 0.075 mmol, 1 eq.), 4Å MS and TMSOTf (42 μL, 0.225 mmol, 3 eq.), sequentially. The reaction was stirred at room temperature or 0 °C for the time listed in Table 2.2.3. The reaction mixture was added into saturated NaHCO$_3$ aqueous solution (5 mL) and extracted with DCM for 3 times. The organic layers were combined and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 33a ~ 43a.

![Chemical structure](image)

(E)-3,3-Dimethyl-4-(methylsulfonyl)-8b-styryl-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

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\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.56 (d, \(J = 8.1\) Hz, 1H), 7.41 – 7.19 (m, 8H), 6.47 (dd, \(J_1 = 27.6\) Hz, \(J_2 = 15.9\) Hz, 2H), 3.98 (s, 1H), 3.66 (d, \(J = 9\) Hz, 1H), 3.19 (d, \(J = 9\) Hz, 1H), 2.75 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 142.6 (C), 135.9 (C), 132.6 (C), 130.9 (CH), 130.6 (CH), 128.7 (CH), 128.2 (CH), 126.7 (CH), 126.3 (CH), 125.6 (CH), 115.5 (CH), 92.4 (C), 80.0 (CH), 77.9 (CH\(_2\)), 44.2 (C), 35.8 (CH\(_3\)), 26.7 (CH\(_3\)), 20.6 (CH\(_3\)). MS (ESI\(^+\)) m/z (M+H\(^+\)) calcd for C\(_{21}\)H\(_{24}\)NO\(_3\)S\(^+\) 370.1477, found 370.1480.

(E)-3,3-Dimethyl-8b-(4-methylstyryl)-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

\(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.55 (d, \(J = 7.8\) Hz, 1H), 7.41 – 7.34 (m, 2H), 7.26 – 7.19 (m, 3H), 7.12 (d, \(J = 8.1\) Hz, 2H), 6.42 (dd, \(J_1 = 30.0\) Hz, \(J_2 = 15.9\) Hz, 2H), 3.97 (s, 1H), 3.64 (d, \(J = 9\) Hz, 1H), 3.18 (d, \(J = 9\) Hz, 1H), 2.74 (s, 3H), 2.33 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 142.7 (C), 138.2 (C), 133.1 (C), 132.6 (C), 130.7 (CH), 130.6 (CH), 129.9 (CH), 129.4 (CH), 126.6 (CH), 126.3 (CH), 125.6 (CH), 115.5 (CH), 92.4 (C), 80.0 (CH), 77.9 (CH\(_2\)), 44.2 (C), 35.8 (CH\(_3\)), 26.7 (CH\(_3\)), 21.2 (CH\(_3\)), 20.6 (CH\(_3\)). MS (ESI\(^+\)) m/z (M+H\(^+\)) calcd for C\(_{22}\)H\(_{26}\)NO\(_3\)S\(^+\) 384.1633, found 384.1634.
(E)-3,3-Dimethyl-8b-(3-methylstyryl)-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.56 (d, $J = 8.1$ Hz, 1H), 7.41 – 7.34 (m, 2H), 7.24 – 7.15 (m, 4H), 7.08 (d, $J = 6.9$ Hz, 1H), 6.45 (dd, $J_1 = 38.7$ Hz, $J_2 = 15.9$ Hz, 2H), 3.98 (s, 1H), 3.65 (d, $J = 9$ Hz, 1H), 3.19 (d, $J = 9$ Hz, 1H), 2.75 (s, 3H), 2.34 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.7 (C), 138.3 (C), 135.8 (C), 132.6 (C), 130.8 (CH), 130.7 (CH), 130.6 (CH), 129.0 (CH), 128.6 (CH), 127.4 (CH), 126.3 (CH), 125.6 (CH), 123.8 (CH), 115.5 (CH), 92.4 (C), 80.0 (CH), 77.9 (CH$_2$), 44.2 (C), 35.8 (CH$_3$), 26.7 (CH$_3$), 21.3 (CH$_3$), 20.6 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{23}$H$_{26}$NO$_3$S$^+$ 384.1633, found 384.1631.

(E)-3,3-Dimethyl-8b-(2-methylstyryl)-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.56 (d, $J = 7.8$ Hz, 1H), 7.44 – 7.36 (m, 3H), 7.25 – 7.12 (m, 4H), 6.72 (d, $J = 15.9$ Hz, 1H), 6.36 (d, $J = 15.9$ Hz, 1H), 3.99 (s, 1H), 3.66 (d, $J = 9$ Hz, 1H), 3.20 (d, $J = 9$ Hz, 1H), 2.75 (s, 3H), 2.24 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 142.7 (C), 135.7 (C), 135.2 (C), 132.7 (C), 132.3 (CH), 130.6 (CH), 130.4 (CH), 128.6 (CH), 128.1 (CH), 126.3 (CH), 126.2 (CH), 125.8 (CH), 125.6 (CH), 115.5 (CH), 92.4 (C), 80.0 (CH), 77.8 (CH$_2$), 44.3 (C), 35.7 (CH$_3$), 26.6 (CH$_3$), 20.6 (CH$_3$), 19.7 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{22}$H$_{26}$NO$_3$S$^+$ 384.1633, found 384.1635.

(\textit{E})-8b-(4-Methoxystyril)-3,3-dimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.55 (d, $J = 8.1$ Hz, 1H), 7.40 – 7.34 (m, 2H), 7.29 (d, $J = 8.7$ Hz, 2H), 7.22 (t, $J = 7.5$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 6.36 (dd, $J_1 = 18$ Hz, $J_2 = 16.8$ Hz, 2H), 3.97 (s, 1H), 3.80 (s, 3H), 3.64 (d, $J = 9$ Hz, 1H), 3.18 (d, $J = 9$ Hz, 1H), 2.74 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 159.7 (C), 142.7 (C), 132.7 (C), 130.5 (CH), 130.2 (CH), 128.7 (CH), 128.6 (C), 127.9 (CH), 126.3 (CH), 125.6 (CH), 115.5 (CH), 114.1 (CH), 92.4 (C), 80.0 (CH), 77.8 (CH$_2$), 55.3 (CH$_3$), 44.2 (C), 35.8 (CH$_3$), 26.7 (CH$_3$), 20.6 (CH$_3$).
(E)-8b-(4-Bromostyryl)-3,3-dimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): δ 7.55 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.41 – 7.32 (m, 2H), 7.23 – 7.19 (m, 3H), 6.44 (dd, $J_1 = 29.3$ Hz, $J_2 = 15.9$ Hz, 2H), 3.98 (s, 1H), 3.64 (d, $J = 9$ Hz, 1H), 3.19 (d, $J = 9$ Hz, 1H), 2.75 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.7 (C), 134.8 (C), 132.3 (C), 131.8 (CH), 131.5 (CH), 130.7 (CH), 129.4 (CH), 128.2 (CH), 126.2 (CH), 125.6 (CH), 122.1 (C), 115.5 (CH), 92.2 (C), 79.8 (CH), 77.9 (CH$_2$), 44.3 (C), 35.9 (CH$_3$), 26.7 (CH$_3$), 20.6 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{21}$H$_{23}$BrNO$_3$S$^+$ 448.0582, found 448.0593.

(E)-3,3-Dimethyl-4-(methylsulfonyl)-8b-(4-(trifluoromethyl)styryl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.59 – 7.55 (m, 3H), 7.47 – 7.33 (m, 4H), 7.22 (t, \(J = 7.5\) Hz, 1H), 6.56 (dd, \(J_1 = 21.3\) Hz, \(J_2 = 15.9\) Hz, 2H), 4.00 (s, 1H), 3.66 (d, \(J = 9\) Hz, 1H), 3.21 (d, \(J = 9\) Hz, 1H), 2.77 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 142.7 (C), 139.3 (C), 133.3 (CH), 132.1 (C), 130.8 (CH), 129.1 (CH), 126.9 (CH), 126.2 (CH), 125.7 (CH), 115.5 (CH), 92.1 (C), 79.8 (CH), 77.9 (CH\(_2\)), 44.3 (C), 35.9 (CH\(_3\)), 26.6 (CH\(_3\)), 20.6 (CH\(_3\)). MS (ESI\(^+\)) m/z (M+H\(^+\)) calcd for C\(_{22}\)H\(_{23}\)F\(_3\)NO\(_3\)S\(^+\) 438.1351, found 438.1352.

3,3-Dimethyl-4-(methylsulfonyl)-8b-((IE,3E)-4-phenylbuta-1,3-dien-1-yl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.55 (d, \(J = 8.1\) Hz, 1H), 7.40 – 7.29 (m, 6H), 7.24 – 7.19 (m, 2H), 6.80 (dd, \(J_1 = 15.6\) Hz, \(J_2 = 9.9\) Hz, 1H), 6.53 (d, \(J = 15.6\) Hz, 1H), 6.24 (dd, \(J_1 = 15.3\) Hz, \(J_2 = 9.9\) Hz, 1H), 6.12 (d, \(J = 15.3\) Hz, 1H), 3.94 (s, 1H), 3.62 (d, \(J = 9\) Hz, 1H), 3.16 (d, \(J = 9\) Hz, 1H), 2.75 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 142.7 (C), 136.7 (C), 134.6 (CH), 134.3 (CH), 132.6 (C), 131.0 (CH), 130.6 (CH), 128.7 (CH), 128.0 (CH), 127.4 (CH), 126.4 (CH), 126.2 (CH), 125.6 (CH), 115.6 (CH), 92.2 (C), 80.1 (CH), 77.8 (CH\(_2\)), 44.2 (C), 35.8 (CH\(_3\)), 26.7 (CH\(_3\)), 20.6 (CH\(_3\)).
(E)-3,3-Dimethyl-4-(methylsulfonyl)-8b-(4-phenylbut-1-en-3-yn-1-yl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J = 8.1$ Hz, 1H), 7.42 – 7.31 (m, 7H), 7.20 (t, $J = 7.5$ Hz, 1H), 6.47 (dd, $J_1 = 27.6$ Hz, $J_2 = 15.9$ Hz, 2H), 6.47 (d, $J = 15.6$ Hz, 1H), 5.89 (d, $J = 15.6$ Hz, 1H), 3.97 (s, 1H), 3.62 (d, $J = 9$ Hz, 1H), 3.18 (d, $J = 9$ Hz, 1H), 2.78 (s, 3H), 1.236 (s, 3H), 1.15 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.1 (CH), 142.6 (C), 131.7 (C), 131.5 (CH), 130.8 (CH), 128.5 (CH), 128.4 (CH), 126.2 (CH), 125.6 (CH), 122.8 (C), 115.5 (CH), 110.8 (CH), 92.1 (C), 91.9 (C), 86.6 (C), 79.6 (CH), 77.9 (CH$_2$), 44.3 (C), 35.7 (CH$_3$), 26.5 (CH$_3$), 20.6 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{23}$H$_{24}$N$_2$O$_3$S$^{+}$ 394.1477, found 394.1471.

(E)-3,3-Dimethyl-4-(methylsulfonyl)-8b-(2-(naphthalen-1-yl)vinyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.90 – 7.79 (m, 3H), 7.60 (d, $J = 7.8$ Hz, 2H), 7.51 – 7.40 (m, 5H), 7.30 – 7.25 (m, 2H), 6.53 (d, $J = 15.9$ Hz, 1H), 4.06 (s, 1H), 3.71 (d, $J = 9$ Hz, 1H), 3.25 (d, $J = 9$ Hz, 1H), 2.79 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 142.8 (C), 134.0 (CH), 133.7 (C), 133.6 (C), 132.6 (C), 131.2 (C), 130.7 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 126.3 (CH), 126.2 (CH), 126.0 (CH), 125.7 (CH), 125.6 (CH), 124.0 (CH), 123.3 (CH), 115.6 (CH), 92.5 (C), 80.0 (CH), 77.9 (CH$_2$), 44.3 (C), 35.7 (CH$_3$), 26.7 (CH$_3$), 20.6 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{25}$H$_{26}$NO$_3$S$^+$ 420.1633, found 420.1633.

3,3-Dimethyl-4-(methylsulfonyl)-8b-((IE,3E)-penta-1,3-dien-1-yl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.51 (d, $J = 8.1$ Hz, 1H), 7.37 – 7.26 (m, 2H), 7.18 (t, $J = 7.5$ Hz, 1H), 6.11 - 5.84 (m, 3H), 5.71 - 5.64 (m, 1H), 3.88 (s, 1H), 3.57 (d, $J = 8.7$ Hz, 1H), 3.11 (d, $J = 8.7$ Hz, 1H), 2.71 (s, 3H), 1.74 (d, $J = 6.6$ Hz, 3H), 1.21 (s, 3H), 1.12 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 142.4 (C), 132.6 (C), 131.6 (CH), 131.5 (CH), 131.0 (CH), 130.3 (CH), 130.1 (CH), 126.0 (CH), 125.3 (CH), 115.3 (CH), 92.0 (C), 79.9 (CH), 77.6 (CH$_2$), 43.9 (C), 35.5 (CH$_3$), 26.5 (CH$_3$), 20.4 (CH$_3$), 18.0 (CH$_3$).
(E)-5,5-Dimethyl-6-(methylsulfonyl)-2-(prop-1-en-1-yl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.07 (m, 1H), 7.42 (m, 1H), 7.33 – 7.30 (m, 2H), 5.82 - 5.72 (m, 1H), 5.65 - 5.57 (m, 1H), 4.50 (m, 1H), 4.01 (d, $J = 12.6$ Hz, 1H), 3.58 (d, $J = 12.6$ Hz, 1H), 3.03 (d, $J = 6.6$ Hz, 2H), 2.73 (s, 3H), 1.72 (d, $J = 6.6$ Hz, 3H), 1.63 (s, 3H), 1.50 (s, 3H).

2.5.3 Preparation of product 33c

3,3,8b-Trimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-$2H$-furo[3,2-6]indole
To a solution of compound 31 (21 mg, 0.075 mmol, 1 eq.) in anhydrous CHCl₃ (1.5 mL) was added TMSOTf (14 μL, 0.075 mmol, 1 eq.). The reaction was stirred at room temperature for 0.5 h. The reaction mixture was added into saturated NaHCO₃ aqueous solution (5 mL) and extracted with DCM for 3 times. The organic layers were combined and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 33c (21 mg, 100% yield). ¹H NMR (300 MHz, CDCl₃): δ 7.48 (d, J = 8.1 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.17 (td, J₁ = 7.5 Hz, J₂ = 0.9 Hz, 1H), 3.78 (s, 1H), 3.51 (d, J = 8.7 Hz, 1H), 3.05 (d, J = 8.7 Hz, 1H), 2.77 (s, 3H), 1.72 (s, 3H), 1.23 (s, 3H), 1.13 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 141.5 (C), 134.5 (C), 130.0 (CH), 125.2 (CH), 124.1 (CH), 114.9 (CH), 89.2 (C), 79.2 (CH), 77.4 (CH₂), 44.1 (C), 35.4 (CH₃), 26.9 (CH₃), 26.6 (CH₃), 20.4 (CH₃). MS (ESI⁺) m/z (M+H)⁺ calcd for C₁₄H₂₀NO₅S⁺ 282.1164, found 282.1165.

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<th>Observed (ppm)</th>
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<tr>
<td>1.72 (s, 3H)</td>
<td>3.78 (s, 1H)</td>
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</tbody>
</table>

2.5.4 Preparation of products 44b ~ 53b

General Procedure: To a solution of compound 31 (21 mg, 0.075 mmol, 1 eq.) in anhydrous CHCl₃ (1.5 mL) was added aldehyde (0.375 mmol, 5 eq.), and anhydrous
ZnCl$_2$ (0.113 mmol, 1.5 eq.). The reaction was stirred at room temperature for 24 h. The reaction mixture was added into ice-water and extracted with DCM for 3 times. The organic layers were combined and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 44b - 53b.

![44b](image)

2-Isopropyl-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.10 – 8.06 (m, 1H), 7.45 – 7.42 (m, 1H), 7.33 – 7.30 (m, 2H), 3.96 (d, $J = 12.6$ Hz, 1H), 3.81 (dd, $J_1 = 11.7$ Hz, $J_2 = 6.3$ Hz, 1H), 3.56 (d, $J = 12.6$ Hz, 1H), 2.94 (d, $J = 6.3$ Hz, 2H), 2.71 (s, 3H), 1.90 – 1.79 (m, 1H), 1.60 (s, 3H), 1.50 (s, 3H), 1.00 (dd, $J_1 = 6.9$ Hz, $J_2 = 4.5$ Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 145.5 (C), 138.5 (C), 131.6 (C), 125.2 (CH), 124.3 (CH), 122.7 (C), 118.3 (CH), 116.4 (CH), 82.3 (CH), 77.9 (CH$_2$), 40.6 (C), 37.7 (CH$_3$), 33.6 (CH), 25.2 (CH$_3$), 25.2 (CH$_2$), 24.2 (CH$_3$), 18.5 (CH$_3$), 18.2 (CH$_3$).
2-Ethyl-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-

b]indole

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.09 – 8.06 (m, 1H), 7.44 – 7.41 (m, 1H), 7.33 – 7.30 (m, 2H), 3.97 – 3.90 (m, 1H), 3.92 (d, $J = 12.6$ Hz, 1H), 3.58 (d, $J = 12.6$ Hz, 1H), 3.04 – 2.86 (m, 2H), 2.69 (s, 3H), 1.73 – 1.55 (m, 2H), 1.60 (s, 3H), 1.51 (s, 3H), 1.01 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 145.6 (C), 138.6 (C), 131.7 (C), 125.2 (CH), 124.3 (CH), 122.5 (C), 118.3 (CH), 116.5 (CH), 78.9 (CH), 78.0 (CH$_2$), 40.7 (C), 37.6 (CH$_3$), 29.5 (CH$_2$), 28.1 (CH$_2$), 25.2 (CH$_3$), 24.2 (CH$_3$), 10.1 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{17}$H$_{24}$NO$_3$S$^+$ 322.1471, found 322.1485.

![Chemical Structure](image)

2-Butyl-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-

b]indole

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.09 – 8.06 (m, 1H), 7.44 – 7.41 (m, 1H), 7.33 – 7.30 (m, 2H), 4.00 (m, 1H), 3.92 (d, $J = 12.6$ Hz, 1H), 3.56 (d, $J = 12.6$ Hz, 1H), 3.03 – 2.86 (m, 2H), 2.69 (s, 3H), 1.75 – 1.32 (m, 6H), 1.60 (s, 3H), 1.50 (s, 3H), 0.92 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 145.6 (C), 138.6 (C), 131.8 (C), 125.2 (CH), 124.3 (CH), 122.6 (C), 118.4 (CH), 116.5 (CH), 78.0 (CH$_2$), 77.6 (CH), 40.7 (C), 37.6 (CH$_3$), 36.5 (CH$_2$), 28.7 (CH$_2$), 27.9 (CH$_2$), 25.1 (CH$_3$), 24.3 (CH$_3$), 22.8 (CH$_2$), 14.1 (CH$_3$).
5,5-Dimethyl-6-(methylsulfonyl)-2-pentyl-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.09 – 8.06 (m, 1H), 7.43 – 7.40 (m, 1H), 7.33 – 7.30 (m, 2H), 4.00 (m, 1H), 3.92 (d, $J = 12.6$ Hz, 1H), 3.56 (d, $J = 12.6$ Hz, 1H), 3.03 – 2.86 (m, 2H), 2.69 (s, 3H), 1.73 – 1.32 (m, 8H), 1.60 (s, 3H), 1.50 (s, 3H), 0.90 (t, $J = 6.5$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 145.6 (C), 138.6 (C), 131.8 (C), 125.2 (CH), 124.3 (CH), 122.6 (C), 118.3 (CH), 116.5 (CH), 78.0 (CH$_2$), 77.6 (CH), 40.7 (C), 37.6 (CH$_3$), 36.7 (CH$_2$), 31.9 (CH$_2$), 28.7 (CH$_2$), 25.4 (CH$_2$), 25.1 (CH$_3$), 24.3 (CH$_3$), 22.6 (CH$_2$), 14.1 (CH$_3$).

2-Hexyl-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole
\[^{1}\text{H}\] NMR (300 MHz, CDCl\(_3\)): \(\delta 8.09 - 8.06 \text{ (m, 1H)}, 7.43 - 7.41 \text{ (m, 1H)}, 7.33 - 7.30 \text{ (m, 2H)}, 4.00 \text{ (m, 1H)}, 3.92 \text{ (d, } J = 12.6 \text{ Hz, 1H)}, 3.56 \text{ (d, } J = 12.6 \text{ Hz, 1H)}, 3.03 - 2.86 \text{ (m, 2H)}, 2.69 \text{ (s, 3H)}, 1.75 - 1.26 \text{ (m, 10H)}, 1.60 \text{ (s, 3H)}, 1.50 \text{ (s, 3H)}, 0.87 \text{ (t, } J = 6.3 \text{ Hz, 3H}). \[^{13}\text{C}\] NMR (75 MHz, CDCl\(_3\)): \(\delta 145.6 \text{ (C), 138.6 (C), 131.8 (C), 125.2 (CH), 124.3 (CH), 122.6 (C), 118.3 (CH), 116.5 (CH), 78.0 (CH\(_2\)), 77.6 (CH), 40.7 (C), 37.5 (CH\(_3\)), 36.8 (CH\(_2\)), 31.8 (CH\(_2\)), 29.4 (CH\(_2\)), 28.7 (CH\(_2\)), 25.7 (CH\(_2\)), 25.1 (CH\(_3\)), 24.3 (CH\(_3\)), 22.6 (CH\(_2\)), 14.1 (CH\(_3\)).

2-Isobutyl-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

\[^{1}\text{H}\] NMR (300 MHz, CDCl\(_3\)): \(\delta 8.09 - 8.06 \text{ (m, 1H)}, 7.43 - 7.40 \text{ (m, 1H)}, 7.33 - 7.30 \text{ (m, 2H)}, 4.08 - 4.04 \text{ (m, 1H)}, 3.90 \text{ (d, } J = 12.6 \text{ Hz, 1H)}, 3.55 \text{ (d, } J = 12.6 \text{ Hz, 1H)}, 3.01 - 2.84 \text{ (m, 2H)}, 2.68 \text{ (s, 3H)}, 1.91 - 1.82 \text{ (m, 1H)}, 1.59 \text{ (s, 3H)}, 1.51 \text{ (s, 3H)}, 1.33 - 1.26 \text{ (m, 2H)}, 0.94 \text{ (d, } J = 6.6 \text{ Hz, 6H}). \[^{13}\text{C}\] NMR (75 MHz, CDCl\(_3\)): \(\delta 145.7 \text{ (C), 138.6 (C), 131.8 (C), 125.2 (CH), 124.4 (CH), 122.7 (C), 118.4 (CH), 116.5 (CH), 78.1 (CH\(_2\)), 75.6 (CH), 45.8 (CH\(_2\)), 40.7 (C), 37.6 (CH\(_3\)), 29.3 (CH\(_2\)), 25.1 (CH\(_3\)), 24.6 (CH), 24.3 (CH\(_3\)), 23.3 (CH\(_3\)), 22.2 (CH\(_3\)).

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2-(sec-Butyl)-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole (diastereomer mixture)

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.09 – 8.06 (m, 1H), 7.44 – 7.42 (m, 1H), 7.33 – 7.30 (m, 2H), 3.98 (d, $J = 12.6$ Hz, 2H), 3.51 (d, $J = 12.6$ Hz, 1H), 3.05 – 2.84 (m, 2H), 2.70 (s, 3H), 1.73 – 1.57 (m, 1H), 1.63 (s, 3H), 1.47 (s, 3H), 1.33 – 1.15 (m, 2H), 1.00 – 0.92 (m, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 145.5 (C), 138.5 (C), 131.6 (C), 125.2 (CH), 124.3 (CH), 123.4 (C), 118.3 (CH), 116.4 (CH), 80.6 (CH), 78.2 (CH$_2$), 40.6 (CH), 40.5 (C), 37.6 (CH$_3$), 25.8 (CH$_2$), 25.6 (CH$_2$), 25.2 (CH$_3$), 24.1 (CH$_3$), 14.5 (CH$_3$), 12.0 (CH$_3$).

5,5-Dimethyl-6-(methylsulfonyl)-2-(pentan-2-yl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole (diastereomer mixture)

$^1$H NMR (300 MHz, CDCl$_3$): δ 8.09 – 8.06 (m, 1H), 7.48 – 7.39 (m, 1H), 7.33 – 7.30 (m, 2H), 4.01 – 3.86 (m, 2H), 3.56 – 3.49 (m, 1H), 3.05 – 2.83 (m, 2H), 2.70 (s, 3H), 1.63
(s, 3H), 1.47 (s, 3H), 1.32 – 1.22 (m, 5H), 0.99 – 0.90 (m, 6H). $^\text{13C}$ NMR (75 MHz, CDCl$_3$): $\delta$ 145.5 (C), 138.5 (C), 131.6 (C), 125.2 (CH), 124.3 (CH), 123.5 (C), 118.4 (CH), 116.4 (CH), 80.9 (CH), 78.2 (CH$_2$), 40.5 (C), 38.7 (CH), 37.6 (CH$_3$), 35.1 (CH$_2$), 25.7 (CH$_2$), 25.4 (CH$_3$), 24.1 (CH$_3$), 20.6 (CH$_2$), 14.8 (CH$_3$), 14.4 (CH$_3$).

![Structure](image)

2-Cyclohexyl-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.09 – 8.06 (m, 1H), 7.45 – 7.42 (m, 1H), 7.33 – 7.30 (m, 2H), 3.96 (d, $J = 12.6$ Hz, 1H), 3.80 (dd, $J_1 = 12$ Hz, $J_2 = 6$ Hz, 1H), 3.52 (d, $J = 12.6$ Hz, 1H), 2.95 (d, $J = 6.6$ Hz, 2H), 2.71 (s, 3H), 1.91 – 1.68 (m, 5H), 1.61 (s, 3H), 1.48 (s, 3H), 1.32 – 1.08 (m, 6H). $^\text{13C}$ NMR (75 MHz, CDCl$_3$): $\delta$ 145.5 (C), 138.5 (C), 131.7 (C), 125.1 (CH), 124.3 (CH), 122.8 (C), 118.3 (CH), 116.4 (CH), 81.8 (CH), 77.9 (CH$_2$), 43.7 (CH), 40.6 (C), 37.7 (CH$_3$), 28.9 (CH$_2$), 28.7 (CH$_2$), 26.6 (CH$_2$), 26.4 (CH$_2$), 26.3 (CH$_2$), 25.5 (CH$_2$), 25.1 (CH$_3$), 24.3 (CH$_3$).
5,5-Dimethyl-6-(methylsulfonyl)-2-phenethyl-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

1H NMR (300 MHz, CDCl3): δ 8.07 – 8.06 (m, 1H), 7.39 – 7.38 (m, 1H), 7.32 – 7.26 (m, 4H), 7.23 – 7.17 (m, 3H), 4.02 – 4.00 (m, 1H), 3.94 (d, J = 7.5 Hz, 1H), 3.60 (d, J = 7.5 Hz, 1H), 3.00 - 2.95 (m, 2H), 2.86 - 2.75 (m, 2H), 2.67 (s, 3H), 2.02 – 1.95 (m, 1H), 1.86 – 1.79 (m, 1H), 1.60 (s, 3H), 1.53 (s, 3H). 13C NMR (75 MHz, CDCl3): δ 145.4 (C), 141.8 (C), 138.4 (C), 131.5 (C), 128.4 (CH), 128.2 (CH), 125.7 (CH), 125.1 (CH), 124.2 (CH), 122.2 (C), 118.2 (CH), 116.3 (CH), 78.0 (CH2), 76.3 (CH), 40.6 (C), 38.3 (CH2), 37.4 (CH3), 31.7 (CH2), 28.7 (CH2), 25.0 (CH3), 24.1 (CH3).

5,5-Dimethyl-6-(methylsulfonyl)-2-phenyl-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.10 (d, \(J = 8.1\) Hz, 1H), 8.08 – 7.28 (m, 8H), 5.16 (dd, \(J_1 = 9.9\) Hz, \(J_2 = 3.3\) Hz, 1H), 4.26 (d, \(J = 12.6\) Hz, 1H), 3.73 (d, \(J = 12.6\) Hz, 1H), 3.33 – 3.15 (m, 2H), 2.76 (s, 3H), 1.72 (s, 3H), 1.56 (s, 3H).

### 2.5.5 Preparation of product 59

\(\text{(E)}\)-8b-(4-Chlorobut-2-en-1-yl)-3,3-dimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2H-furo[3,2-b]indole

To a solution of compound 31 (21 mg, 0.075 mmol, 1 eq.) in anhydrous CHCl\(_3\) (1.5 mL) was added aldehyde 58 (28.6 \(\mu\)L, 0.375 mmol, 5 eq.), and anhydrous ZnCl\(_2\) (15.4 mg, 0.113 mmol, 1.5 eq.). The reaction was stirred at room temperature for 24 h. The reaction mixture was added into ice-water and extracted with DCM for 3 times. The organic layers were combined and dried over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under
reduced pressure and the residue was submitted to chromatography to afford the corresponding product 59 (26.6 mg, 100% yield). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.47 (d, $J = 8.1$ Hz, 1H), 7.36 – 7.30 (m, 2H), 7.16 (t, $J = 7.4$ Hz, 1H), 5.61 – 5.52 (m, 1H), 5.45 – 5.35 (m, 1H), 3.87 (s, 3H), 3.53 – 3.47 (m, 3H), 3.09 (d, $J = 8.7$ Hz, 1H), 2.81 - 2.71 (m, 2H), 2.77 (s, 3H), 2.46 – 2.37 (m, 2H), 1.19 (s, 3H), 1.12 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.1 (C), 133.1 (C), 131.0 (CH), 130.4 (CH), 127.9 (CH), 125.1 (CH), 124.7 (CH), 114.5 (CH), 77.6 (CH$_2$), 76.3 (CH), 44.1 (C), 43.8 (CH$_2$), 42.9 (CH$_2$), 36.3 (CH$_3$), 35.7 (CH$_2$), 26.6 (CH$_3$), 20.8 (CH$_3$). MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{18}$H$_{25}$ClNO$_3$S$^+$ 370.1238, found 370.1226.

2.5.6 Materials and Methods in Computational Study

We employ DFT methods to investigate the electronic structure and energetics along the reaction potential energy surface (PES), where the effect of solvent is considered with the polarizable continuum medium (PCM) model. All calculations are performed with Gaussian 09 software package.$^{20}$

The geometries discussed in this work are fully optimized in gas phase at M06/6-31+G*. Frequency calculations are carried out to confirm the nature of the stationary points. The zero-point energies and the thermal correction at 298.15K and 1 atm are obtained with the harmonic approximation at optimized structures. The PCM model, SMD$^{21}$, is employed to evaluate the influence of solvent on the PES with single point calculation at M06/6-311+G**$^{22}$ level. Solvent effect is taken into account in relative energies discussed in this work without exception.
2.6 References


Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.


3. Highly Efficient and Stereoselective Synthesis of (Z)-β-Fluoro Enals from Alkynals and Applications in Synthesis

3.1 Introduction

Fluorination reaction has become a widespread and important strategy to introduce fluorine atoms into pharmaceutics and bioactive compounds with significant improving drug properties in many cases, such as 5-fluorouracil (5-FU, 1) and atorvastatin (Lipitor, 2).\textsuperscript{1} Compared to hydrogen, fluorine is much more electronegative but has a similar small size.\textsuperscript{2} Incorporating fluorine atoms increases lipophilicity, improves its partitioning into membranes and hence increases bioavailability.\textsuperscript{2,3} Moreover, the strong C-F bond resists deactivation in the liver by cytochrome P450 oxidases reducing drug metabolism.\textsuperscript{4} Therefore, fluorine and fluorinated substituents are attractive bioisosteres.

Among various fluorinated substituents, fluoroalkene (C=CF) has been widely used as a replacement for the peptide bond in the field of medicinal chemistry.\textsuperscript{5} Fluorine takes the position of the carbonyl O, and the planarity of the vinyl unit makes it quite a good match in size and geometry of the amide backbone (Figure 3.1.2). Contrary to such similarities, fluoroalkene moiety would be a non-hydrolyzable both chemically and
enzymatically. The lack of rotational freedom of fluoroalkene is also a different property from that of an amide bond. Because of these unique properties, fluoroalkene isosteres are utilized as non-hydrolyzable and/or conformationally restricted replacements for the parent amide bonds. In addition, fluoroalkenes can also serve as useful building blocks in the synthesis of fluorinated compounds.

![Dipeptide and its fluoroalkene bioisostere](image)

**Figure 3.1.2 Dipeptide and its fluoroalkene bioisostere 5**

### 3.2 Research Design

Fluoroalkenes are generally obtained in multi-step synthetic sequences. For example, dihalide compound 7 is usually synthesized in advance to generate fluoroalkene 8 (Scheme 3.2.1).

![Multi-step synthesis of fluoroalkene](image)

**Scheme 3.2.1 Example of multi-step synthesis of fluoroalkene**

In this context, the direct addition of HF to alkynes should be a very attractive strategy. However, examples reported in this area are extremely rare. In 1985, Patrice Albert and Jack Cousseau carried out an addition of HF to alkynes using
tetrabutylammonium and polymer-supported dihydrogen trifluoride reagents (Scheme 3.2.2).\textsuperscript{8} However, a mixture of the Z- and E-isomers of the fluoro-adducts was obtained. Recently, a gold-catalyzed trans-hydrofluorination of alkynes was reported (Scheme 3.2.3).\textsuperscript{9} But this method is limited in the scope to symmetric internal alkynes. When electron-rich aryl substituent was employed, poor regioselectivity between α- and β-fluorination was observed.

![Scheme 3.2.2 HF addition to alkynes using nBu\textsubscript{4}N\textsuperscript{+}H\textsubscript{2}F\textsubscript{3} or P\textsuperscript{+}H\textsubscript{2}F\textsubscript{3}\textsuperscript{-}]

Recent studies from our group\textsuperscript{10} and others\textsuperscript{11} reveal that alkynals can be activated by a secondary amine catalyst via iminium ion intermediate, which renders nucleophilic attack on the β-position. Based on these studies, we devised a new secondary amine catalyzed HF addition to alkynals (Scheme 3.2.4). It is hypothesized that activation of ynal 16 via iminium ion 19 is followed by the nucleophilic attack from fluorine on the β-position. Trans-addition of proton to the allenamine 20 gives a new iminium ion 21. Then hydrolysis of 21 generates fluoroalkene 18.
3.3 Results and Discussion

We commenced our study by screening secondary amine catalysts for the HF addition to phenylpropiolaldehyde (16a) using HF-pyridine (17) as fluorination source (Table 3.3.1).

Table 3.3.1 Optimization of reaction conditions for HF addition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>t-BuOMe</td>
<td>None</td>
<td>7</td>
<td>70</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>II</td>
<td>t-BuOMe</td>
<td>None</td>
<td>72</td>
<td>&lt; 10</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>t-BuOMe</td>
<td>None</td>
<td>72</td>
<td>&lt; 10</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>t-BuOMe</td>
<td>0.8 equiv. DABCO</td>
<td>24</td>
<td>100</td>
<td>decomposed</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>t-BuOMe</td>
<td>0.5 equiv. TEA</td>
<td>72</td>
<td>100</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>t-BuOMe</td>
<td>1.0 equiv. TEA</td>
<td>36</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----</td>
<td>-------</td>
<td>-----------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>7</td>
<td>I</td>
<td>t-BuOMe</td>
<td>1.0 equiv. pyridine</td>
<td>24</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>t-BuOMe</td>
<td>0.5 equiv. NaHCO₃</td>
<td>72</td>
<td>&lt; 10</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>I</td>
<td>t-BuOMe</td>
<td>1.2 equiv. Na₂CO₃</td>
<td>72</td>
<td>&lt; 10</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>I</td>
<td>t-BuOMe</td>
<td>1.2 equiv. KOAc</td>
<td>72</td>
<td>&lt; 10</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>I</td>
<td>Acetone</td>
<td>1.2 equiv. pyridine</td>
<td>72</td>
<td>100</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>I</td>
<td>CH₃CN</td>
<td>1.2 equiv. pyridine</td>
<td>72</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>I</td>
<td>EtOAc</td>
<td>1.2 equiv. pyridine</td>
<td>72</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>14</td>
<td>I</td>
<td>EtOAc</td>
<td>1.2 equiv. pyridine</td>
<td>4 h</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>15</td>
<td>I</td>
<td>EtOAc</td>
<td>1.0 equiv. pyridine</td>
<td>4 h</td>
<td>100</td>
<td>63</td>
</tr>
<tr>
<td>16</td>
<td>I</td>
<td>EtOAc</td>
<td>0.8 equiv. pyridine</td>
<td>1 h</td>
<td>100</td>
<td>82</td>
</tr>
<tr>
<td>17</td>
<td>I</td>
<td>EtOAc</td>
<td>0.5 equiv. pyridine</td>
<td>96 h</td>
<td>100</td>
<td>60</td>
</tr>
</tbody>
</table>

* The reactions were carried out on a 0.1-mmol scale of 16a and monitored by appearance of 18a by TLC and ¹H NMR spectroscopy. § Isolated yields.

Table 3.3.1 summarizes the results of the study in which various catalysts, solvents, additives and reaction time were conducted. Among the three catalysts screened, catalyst I was found to be the best (Table 3.3.1, entry 1). Most of 16a was left unreacted when using catalysts II and III (Table 3.3.1, entries 2 and 3). Based on the proposed mechanism (Scheme 3.2.4), basic conditions should favor the conjugate addition. Therefore, the reaction was treated with some organic (Table 3.3.1, entries 4 to 7) and inorganic bases (Table 3.3.1, entries 8 to 10). Inorganic bases retarded the HF addition process while organic bases accelerated it. Pyridine was found to be the optimal additive to the reaction (Table 3.3.1, entry 7). When the reaction was run in EtOAc, an increased yield of 58% was obtained (Table 3.3.1, entry 13). Next, the amount of pyridine and the reaction time were tuned. The reaction with 0.8 equivalent of pyridine stirring at room temperature for 1 hour delivered 18a in the Z-conformation, exclusively, with an excellent yield of 82% (Table 3.3.1, entry 16).
Having established the optimal conditions for HF addition, we examined the alkynal scope (Table 3.3.2). The reaction went smoothly with both electron-donating and electron-withdrawing substituents at para- and meta-position of benzene ring (Table 3.3.2, entries 1 to 8). However, when ortho-position was occupied, the yield decreased significantly. The reaction also worked well with heterocycles (Table 3.3.2, entries 10, 11 and 13) and fused ring system (Table 3.3.2, entry 12).

Table 3.3.2 Substrate Scope of Alkynals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynal</th>
<th>R</th>
<th>t (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16b</td>
<td>4-FC₆H₄</td>
<td>1</td>
<td>18b</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>16c</td>
<td>4-ClC₆H₄</td>
<td>1</td>
<td>18c</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>16d</td>
<td>4-BrC₆H₄</td>
<td>1</td>
<td>18d</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>16e</td>
<td>4-NO₂C₆H₄</td>
<td>1</td>
<td>18e</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>16f</td>
<td>4-MeC₆H₄</td>
<td>2</td>
<td>18f</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>16g</td>
<td>4-OMeC₆H₄</td>
<td>4</td>
<td>18g</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>16h</td>
<td>3-MeC₆H₄</td>
<td>2</td>
<td>18h</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>16i</td>
<td>3-CF₃C₆H₄</td>
<td>1</td>
<td>18i</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>16j</td>
<td>2-F C₆H₄</td>
<td>1</td>
<td>18j</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>16k</td>
<td>3-pyridinyl</td>
<td>1</td>
<td>18k</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>16l</td>
<td>N-Ts-3-indolyl</td>
<td>1.5</td>
<td>18l</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>16m</td>
<td>2-naphthalenyl</td>
<td>1</td>
<td>18m</td>
<td>66</td>
</tr>
<tr>
<td>13</td>
<td>16n</td>
<td>2-thiophenyl</td>
<td>2.5</td>
<td>18n</td>
<td>79</td>
</tr>
</tbody>
</table>

The reactions were carried out on a 0.1-mmol scale of 16 and monitored by appearance of 18 by TLC and ¹HNMR spectroscopy. Isolated yields.
3.4 Synthetic Applications

Our next focus was directed towards the utilization of Z-fluoroalkenes in the synthesis of new fluorinated compounds.

3.4.1 Reactions Based on Aldehyde Functionality

Scheme 3.4.1.1 Reactions based on aldehyde functionality
Scheme 3.4.1.1 summarizes the reactions carried out with aldehyde group of β-fluoroenal 18a. β-Fluoroenal 18a can be reduced by NaBH₄ to deliver alcohol 22 in a quantitative yield. The Wittig reaction of β-fluoroenal 18a generated fluoro-diene 23 in a yield of 64.2%. When β-fluoroenal 18a was treated with Pd(OAc)₂, aldehyde group was removed and a fluoroalkene 24 was obtained in a good yield. Notably, fluoroalkene 24 could be converted into a microbial tyramine oxidase inhibitor 25 according to the process reported. The Henry reaction of β-fluoroenal 18a with CH₃NO₂ under the base generated compound 27 in a good yield.

![Scheme 3.4.1.2 Reaction of 18a with 28](image)

Interestingly, when β-fluoroenal 18a was treated with secondary amine 28, fluorine was lost and enamine 29 was obtained in a quantitative yield (Scheme 3.4.1.2). The loss of fluorine atom might result from nucleophilic substitution by hydroxyl group of iminium ion 30.
3.4.2 Reactions Based on C=C Bonds

It is known that the C-F bond is the strongest single bond that carbon can form.\textsuperscript{12} In general, the currently known functionalization processes of C–F bond often lose the fluorine atom.\textsuperscript{13} Therefore, the functionalization of C–F bonds is a challenging task that has drawn much attention.

Sharpless epoxidation is known as a reliable protocol to generate epoxide from alkenes. The mild conditions employed in the Sharpless epoxidation may be able to leave C-F bond untouched. When alcohol 22 underwent the Sharpless epoxidation, fluoro-epoxide 32 was obtained as expected, in a good yield and 34\% ee (Scheme 3.4.2.1).

![Scheme 3.4.2.1 Sharpless epoxidation of alcohol 22](image)

Monofluorocyclopropanes elicit significant interest in medicinal chemistry, agrochemistry and liquid crystals as they combine the advantages of organofluorine compounds with the added structural rigidity and metabolic stability of cyclopropanes.\textsuperscript{14} However, limited studies have been carried out for their synthesis.\textsuperscript{15} The most popular strategy to synthesize this moiety is to utilize the Simmons-Smith reaction. Monofluorocyclopropane 34 was successfully generated from alcohol 22 under the conditions of the Simmons-Smith reaction (Scheme 3.4.2.1).
Another strategy to prepare monofluorocyclopropane is to utilize the reaction of TBS protected compound 35 with ethyl diazoacetate (36). The desired product 37 was prepared in an excellent yield and high diastereoselectivity using Rh$_2$(OAc)$_4$ as the catalyst (Scheme 3.4.2.3). Deprotection of compound 37 with TBAF resulted in removal of the TBS group as well as the ethyl group.

\[
\text{Simmons-Smith reaction of alcohol } 22
\]
3.5 Conclusions

In summary, we have developed a novel highly efficient and stereoselective direct addition of F anion to alkynals catalyzed by a secondary amine. The β-fluoroenals are generated stereoselectively with Z-geometry. A variety of ynals can be applied for this conjugate addition process. Furthermore, we also have demonstrated the synthetic utilities of Z-β-fluoroenals for the preparation of new valuable fluorinated compounds by elaboration of aldehyde and C=C bond functionalities including reduction, Henry, Wittig, decarbonylation of the aldehyde and cyclopropanation of the C=C bond.

3.6 Experimental Section

General Information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F254 were used for thin-layer chromatography (TLC) analysis. Visualisation was effected with ultraviolet light, potassium permanganate or 2,4-dinitrophenylhydrazine as appropriate. $^1$H, 1D-NOE and $^{13}$CNMR spectra were recorded on a Bruker Avance III 300 unless otherwise stated. CDCl$_3$ (δ = 7.26 and 77.0 for $^1$H and $^{13}$CNMR spectra respectively), DMSO-d$_6$ (δ = 2.50 and 39.5 for $^1$H and $^{13}$CNMR spectra respectively) and perfluorobenzene (δ = 164.9 for $^{19}$FNMR spectra) were used as references. Data for $^1$H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for $^{13}$C NMR are reported as ppm. Multiplicities of carbons were determined by DEPT and comparison with similar compounds. Mass spectra were recorded using a Waters/Micromass LCT Premier instrument.
3.6.1 Preparation of alkynal substrates

3.6.1.1 Procedure for preparation of 16a and 16g

**General Procedure:** To a well-stirred solution of alkyne 39 (60 mmol) in anhydrous THF (150 mL) was added a solution of n-BuLi in hexanes (1.6 M, 41.3 mL, 66 mmol) at -40 °C. The reaction mixture was stirred 15 min at -40 °C, and then anhydrous DMF (9.3 mL, 120 mmol) was added in one portion. The mixture was allowed to slowly reach rt. After stirred for further 30 min, the reaction mixture was quenched by pouring into a biphasic mixture of KH$_2$PO$_4$ (30 g, 220 mmol) in H$_2$O (270 mL) and EtOAc (300 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc for 3 times. The organic layers were combined, washed with brine, dried over anhydrous Na$_2$SO$_4$, and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 16.

![Chemical structure of 3-Phenylnopropiopaldehyde](image)
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 9.43\) (s, 1H), 7.61 (d, \(J = 7.5\) Hz, 2H), 7.50 (t, \(J = 7.5\) Hz, 1H), 7.41 (t, \(J = 7.5\) Hz, 2H).

\begin{center}
\includegraphics[width=0.2\textwidth]{16g.png}
\end{center}

3-(4-Methoxyphenyl)propionaldehyde

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 9.40\) (s, 1H), 7.57 (d, \(J = 8.0\) Hz, 2H), 6.92 (d, \(J = 8.0\) Hz, 2H), 3.86 (s, 3H).

3.6.1.2 Procedure for preparation of 16k and 16n

\[
\begin{align*}
\text{RX} & \quad + \quad \text{propargyl alcohol} \\
40, X=\text{Br or I} & \quad \text{Pd(PPh}_3\text{)}_4, \text{Cul} \\
\text{THF, TEA} & \quad \rightarrow \\
\text{41} & \quad \rightarrow \\
\text{42} & \quad \rightarrow \\
\text{42} & \quad \rightarrow \\
\end{align*}
\]

**General Procedure:** To a well-stirred mixture of halide 40 (1 mmol), Pd(PPh\(_3\))\(_4\) (58 mg, 0.05 mmol) and CuI (19 mg, 0.1 mmol) in TEA (671 \(\mu\)L, 4.8 mmol) and anhydrous THF (2 mL) was added propargyl alcohol (89 \(\mu\)L, 1.5 mmol) at rt. The reaction mixture was stirred under the conditions listed below. The mixture was then filtered through a Celite pad. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding alcohol 42.
To a solution of alcohol 42 (0.75 mmol) in DMSO (1 mL) was added IBX (700 mg, 1.13 mmol). The reaction mixture was stirred at rt for 0.5 h, and then poured into ice-water, extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 16.

3-(Pyridin-3-yl)prop-2-yn-1-ol

3-Bromo-pyridine was used as the starting material. The coupling reaction was stirred at 50 °C for 24 h. $^1$H NMR (300 MHz, CDCl$_3$): δ 8.71 (s, 1H), 8.54 (d, $J = 4.5$ Hz, 1H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.27-7.23 (m, 1H), 4.52 (d, $J = 5.7$ Hz), 2.05 (t, $J = 5.7$ Hz).

3-(Pyridin-3-yl)propiolaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.45 (s, 1H), 8.84 (d, $J = 1.2$ Hz, 1H), 8.70 (dd, $J_1 = 4.8$ Hz, $J_2 = 1.7$ Hz, 1H), 7.90 (dt, $J_1 = 8.1$ Hz, $J_2 = 1.9$ Hz, 1H), 7.37 (ddd, $J_1 = 8.1$ Hz, $J_2 = 4.8$ Hz, $J_3 = 0.9$ Hz, 1H).
3-(Thiophen-2-yl)prop-2-yn-1-ol

2-Iodo-thiphene was used as the starting material. The coupling reaction was stirred at rt for 0.5 h. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.27 (d, $J = 3.6$ Hz, 1H), 7.22 (d, $J = 3.6$ Hz, 1H), 6.97 (dd, $J_1 = 5.1$ Hz, $J_2 = 3.6$ Hz, 1H), 4.51 (d, $J = 5.7$ Hz), 1.66 (t, $J = 5.7$ Hz).

3-(Thiophen-2-yl)propiolaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.41 (s, 1H), 7.57-7.54 (m, 2H), 7.10 (t, $J = 4.5$ Hz, 1H).

3.6.1.3 Procedure for preparation of 16m
3-(Naphthalen-2-yl)prop-2-yn-1-ol

To a well-stirred mixture of bromide 40m (414 mg, 2 mmol), PdCl_2(PPh_3)_2 (70 mg, 0.1 mmol) and CuI (19 mg, 0.1 mmol) in TEA (1.3 mL, 9.6 mmol) and anhydrous THF (4 mL) was added propargyl alcohol (175 μL, 3 mmol) at rt. The reaction mixture was refluxed for 12 h. The mixture was then filtered through a Celite pad. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding alcohol 42m in 74% yield. ^1H NMR (300 MHz, CDCl_3): δ 7.97 (s, 1H), 7.83-7.80 (m, 3H), 7.51-7.47 (m, 3H), 4.56 (d, J = 5.7 Hz), 1.71 (t, J = 5.7 Hz).

3-(Naphthalen-2-yl)propiolaldehyde

To a solution of alcohol 42m (100 mg, 0.55 mmol) in DCM (2 mL) was added activated MnO_2 (530 mg, 5.5 mmol). The reaction mixture was stirred at rt for 4 h. The mixture was filtered through a Celite pad and the solvent was removed under reduced pressure. The residue was submitted to chromatography to afford alkynal 16m (81 mg, 82%
yield). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.48 (s, 1H), 8.19 (s, 1H), 7.86 (d, $J = 8.4$ Hz, 3H), 7.61-7.55 (m, 3H).

3.6.2 Preparation of $\beta$-fluoroenals 18a-18m

![Chemical Structure](image)

**General Procedure:** To a solution of alkynal 16 (0.1 mmol), pyridine (6.5 $\mu$L, 0.08 mmol) and cat. I (5.1 mg, 0.02 mmol) in EtOAc (1 mL) was added HF-Py 17 (7.8 $\mu$L, 0.3 mmol) at rt. The reaction mixture was stirred at rt for the time listed in Table 3.3.2. Then, the reaction mixture was poured into ice-water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na$_2$SO$_4$, and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product 18.

![Chemical Structure](image)

(Z)-3-fluoro-3-phenylacrylaldehyde
\[ ^1H \text{NMR (300 MHz, CDCl}_3\) : \delta 10.19 (d, J = 7.5 Hz, 1H), 7.60 (d, J = 7.8 Hz, 2H), 7.55-7.45 (m, 3H), 6.10 (dd, J_1 = 33.6 Hz, J_2 = 7.5 Hz, 1H). \]

\[ ^13C \text{NMR (75 MHz, CDCl}_3\) : \delta 188.7 (d, J = 12.0 Hz, CH), 171.5 (d, J = 273.8 Hz, C), 132.5 (CH), 129.4 (d, J = 25.5 Hz, C), 129.1 (CH), 126.0 (d, J = 8.3 Hz, CH), 107.3 (d, J = 5.3 Hz, CH). \]

(Z)-3-fluoro-3-(4-fluorophenyl)acrylaldehyde

\[ ^1H \text{NMR (300 MHz, CDCl}_3\) : \delta 10.17 (d, J = 7.5 Hz, 1H), 7.73-7.68 (m, 2H), 7.17 (t, J = 8.6 Hz, 2H), 6.04 (dd, J_1 = 33.9 Hz, J_2 = 7.5 Hz, 1H). \]

\[ ^13C \text{NMR (75 MHz, CDCl}_3\) : \delta 188.5 (d, J = 11.9 Hz, CH), 170.5 (d, J = 273.1 Hz, C), 165.2 (d, J = 253.6 Hz, C), 128.4 (t, J = 8.7 Hz, CH), 125.7 (d, J = 23.3 Hz, C), 116.5 (d, J = 22.3 Hz, CH), 107.1 (d, J = 4.1 Hz, CH). \]

(Z)-3-(4-chlorophenyl)-3-fluoroacrylaldehyde

\[ ^1H \text{NMR (300 MHz, CDCl}_3\) : \delta 10.18 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 6.07 (dd, J_1 = 33.6 Hz, J_2 = 7.5 Hz, 1H). \]

\[ ^13C \text{NMR (125 MHz, CDCl}_3\) : \delta \]

128
CDCl₃): δ 188.4 (d, J = 11.8 Hz, CH), 170.3 (d, J = 273.0 Hz, C), 138.8 (C), 129.5 (CH), 127.9 (d, J = 26.3 Hz, C), 127.2 (d, J = 8.3 Hz, CH), 107.5 (d, J = 5.3 Hz, CH).

(Z)-3-(4-bromophenyl)-3-fluoroacrylaldehyde

¹H NMR (500 MHz, CDCl₃): δ 10.18 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.56 (dd, J₁ = 6.8 Hz, J₂ = 1.8 Hz, 2H), 6.08 (dd, J₁ = 34.0 Hz, J₂ = 7.5 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 181.4 (d, J = 12.5 Hz, CH), 162.3 (d, J = 272.5 Hz, C), 125.4 (C, CH), 121.2 (d, J = 26.3 Hz, C), 120.2 (d, J = 7.5 Hz, CH), 100.5 (d, J = 3.8 Hz, CH).

(Z)-3-fluoro-3-(4-nitrophenyl)acrylaldehyde

¹H NMR (300 MHz, CDCl₃): δ 10.23 (d, J = 7.2 Hz, 1H), 8.34 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 9.0 Hz, 2H), 6.08 (dd, J₁ = 33.9 Hz, J₂ = 7.2 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 188.0 (d, J = 11.3 Hz, CH), 168.5 (d, J = 273.3 Hz, C), 149.8 (C), 135.2 (d, J = 27.0 Hz, C), 126.9 (d, J = 8.0 Hz, CH), 124.3 (CH), 109.7 (d, J = 5.0 Hz, CH).
(Z)-3-fluoro-3-(p-tolyl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.17 (d, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 6.05 (dd, $J_1 = 33.9$ Hz, $J_2 = 7.5$ Hz, 1H), 2.42 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.8 (d, $J = 12.0$ Hz, CH), 171.8 (d, $J = 273.5$ Hz, C), 143.4 (C), 129.8 (CH), 126.6 (d, $J = 25.6$ Hz, C), 126.0 (d, $J = 8.5$ Hz, CH), 106.6 (d, $J = 4.6$ Hz, CH), 21.6 (CH$_3$).

(Z)-3-fluoro-3-(4-methoxyphenyl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.14 (d, $J = 7.5$ Hz, 1H), 7.65 (d, $J = 9.0$ Hz, 2H), 6.97 (d, $J = 9.0$ Hz, 2H), 5.99 (dd, $J_1 = 34.0$ Hz, $J_2 = 7.5$ Hz, 1H), 3.88 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 188.7 (d, $J = 12.0$ Hz, CH), 171.7 (d, $J = 272.3$ Hz, C), 163.1 (C), 128.0 (d, $J = 9.0$ Hz, CH), 121.6 (d, $J = 25.5$ Hz, C), 114.6 (CH), 105.7 (d, $J = 4.5$ Hz, CH), 55.5 (CH$_3$).
(Z)-3-fluoro-3-(m-tolyl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.19 (d, $J = 7.5$ Hz, 1H), 7.51-7.49 (m, 2H), 7.40-7.35 (m, 2H), 6.08 (dd, $J_1 = 33.6$ Hz, $J_2 = 7.5$ Hz, 1H), 2.42 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.8 (d, $J = 11.6$ Hz, CH), 171.8 (d, $J = 274.1$ Hz, C), 138.9 (C), 133.3 (CH), 129.3 (d, $J = 25.9$ Hz, C), 129.0 (CH), 126.5 (d, $J = 7.3$ Hz, CH), 123.2 (d, $J = 7.4$ Hz, CH), 107.2 (CH), 21.4 (CH$_3$).

(Z)-3-fluoro-3-(3-(trifluoromethyl)phenyl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.23 (d, $J = 7.5$ Hz, 1H), 7.95 (s, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.64 (t, $J = 8.0$ Hz, 1H), 6.16 (dd, $J_1 = 33.6$ Hz, $J_2 = 7.5$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 188.2 (d, $J = 11.6$ Hz, CH), 169.6 (d, $J = 273.4$ Hz, C), 132.5, 132.1, 131.7, 130.6, 130.3, 129.8, 129.1, 128.9, 128.9, 128.8, 125.2, 122.8, 122.7, 121.6, 108.3 (d, $J = 5.0$ Hz, CH).
(Z)-3-fluoro-3-(2-fluorophenyl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.24 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, 1H), 7.73 (td, $J_1$ = 7.8 Hz, $J_2$ = 1.5 Hz, 1H), 7.56-7.48 (m, 1H), 7.32-7.16 (m, 2H), 6.29 (dd, $J_1$ = 35.7 Hz, $J_2$ = 7.5 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 189.0 (d, $J = 13.3$ Hz, CH), 166.1 (d, $J = 270.0$ Hz, C), 160.6 (dd, $J_1 = 255.8$ Hz, $J_2 = 6.8$ Hz, C), 133.7 (d, $J = 9.2$ Hz, CH), 127.9 (d, $J = 10.2$ Hz, CH), 117.8 (dd, $J_1 = 27.8$ Hz, $J_2 = 9.9$ Hz, C), 116.7 (d, $J = 22.1$ Hz, CH), 112.4 (dd, $J_1$ = 14.3 Hz, $J_2$ = 3.89 Hz, CH).

(Z)-3-fluoro-3-(pyridin-3-yl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.21 (d, $J = 7.5$ Hz, 1H), 8.96 (s, 1H), 8.76 (d, $J = 4.2$ Hz, 1H), 7.98 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.5$ Hz, 1H), 7.44 (dd, $J_1 = 8.1$ Hz, $J_2 = 5.0$ Hz, 1H), 6.14 (dd, $J_1 = 33.9$ Hz, $J_2 = 7.5$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 187.9 (d, $J = 11.5$ Hz, CH), 168.9 (d, $J = 273.7$ Hz, C), 152.7 (CH), 147.0 (d, $J = 8.6$ Hz, CH), 133.0 (d, $J = 7.8$ Hz, CH), 125.6 (d, $J = 26.2$ Hz, C), 123.6 (CH), 108.3 (d, $J = 4.4$ Hz, CH).
(Z)-3-fluoro-3-(1-tosyl-1H-indol-3-yl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): δ 10.20 (d, $J = 7.5$ Hz, 1H), 8.14 (s, 1H), 8.03 (d, $J = 8.1$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 7.8$ Hz, 1H), 7.46-7.34 (m, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 6.05 (dd, $J_1 = 35.0$ Hz, $J_2 = 7.5$ Hz, 1H), 2.38 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 188.2 (d, $J = 12.2$ Hz, CH), 167.0 (d, $J = 267.8$ Hz, C), 146.1 (C), 135.3 (C), 134.4 (C), 130.3 (CH), 128.5 (d, $J = 8.5$ Hz, CH), 127.2 (CH), 126.0 (CH), 125.6 (d, $J = 6.8$ Hz, C), 124.7 (CH), 120.6 (CH), 114.0 (CH), 112.8 (d, $J = 28.3$ Hz, C), 108.5 (d, $J = 4.1$ Hz, CH), 21.7 (CH$_3$).

(Z)-3-fluoro-3-(naphthalen-2-yl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): δ 10.25 (d, $J = 7.5$ Hz, 1H), 8.27 (s, 1H), 7.95-7.87 (m, 3H), 7.66-7.55 (m, 3H), 6.22 (dd, $J_1 = 33.9$ Hz, $J_2 = 7.5$ Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 188.6 (d, $J = 12.2$ Hz, CH), 171.3 (d, $J = 273.2$ Hz, C), 134.8 (C), 132.5 (C), 129.0 (CH), 128.9 (CH), 128.4 (CH), 127.7 (CH), 127.2 (CH), 126.9 (d, $J = 8.9$ Hz, CH), 126.4 (d, $J = 24.9$ Hz, C), 121.7 (d, $J = 7.8$ Hz, CH), 107.5 (d, $J = 5.0$ Hz, CH).
(Z)-3-fluoro-3-(thiophen-2-yl)acrylaldehyde

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 10.11 (d, $J = 7.5$ Hz, 1H), 7.59-7.58 (m, 2H), 7.18-7.15 (m, 1H), 5.92 (dd, $J_1 = 33.3$ Hz, $J_2 = 7.8$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 180.8 (d, $J = 10.5$ Hz, CH), 159.6 (d, $J = 269.6$ Hz, C), 125.6 (d, $J = 30.8$ Hz, C), 124.4 (CH), 122.9 (d, $J = 4.8$ Hz, CH), 121.6 (CH), 99.1 (d, $J = 4.1$ Hz, CH).

3.6.3 Derivatization of compound 18a

3.6.3.1 Reactions Based on Aldehyde Functionality of 18a
(Z)-3-fluoro-3-phenylprop-2-en-1-ol

To a solution of aldehyde 18a (92.6 mg, 0.62 mmol) in MeOH (2 mL) was added NaBH₄ (24 mg, 0.62 mmol) in some portions slowly within 30 min at 0 °C. The reaction was stirred at rt for 30 min. Brine 10 mL was added and extracted with EtOAc for three times. The organic layers were combined and dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was submitted to chromatography to afford the alcohol 22 in 95% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.56-7.53 (m, 2H), 7.39-7.37 (m, 3H), 5.67 (dt, J₁ = 36.6 Hz, J₂ = 7.1 Hz, 1H), 4.45 (dd, J₁ = 7.1 Hz, J₂ = 2.0 Hz, 2H).

(2E,4Z)-ethyl 5-fluoro-5-phenylpenta-2,4-dienoate

To a stirred solution of aldehyde 18a (20.6 mg, 0.137 mmol) in PhCH₃ (1 mL) was added Ph₃P=CHCO₂Et (62 mg, 0.178 mmol). The resulting mixture was stirred at rt for 1 h, and then poured into water. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford product 23 in 64% yield. ¹H NMR (300 MHz, CDCl₃): δ 7.77
(dd, $J_1 = 15.6$ Hz, $J_2 = 11.4$ Hz, 1H), 7.63-7.60 (m, 2H), 7.42-7.40 (m, 3H), 6.22 (dd, $J_1 = 33.3$ Hz, $J_2 = 11.4$ Hz, 1H), 5.99 (d, $J = 15.6$ Hz, 1H), 4.24 (dd, $J_1 = 14.3$ Hz, $J_2 = 7.1$ Hz, 2H), 1.32 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 166.7, 162.9, 159.4, 136.1, 136.0, 130.9, 130.6, 130.2, 128.6, 124.7, 124.6, 120.9, 120.8, 104.3, 104.1, 60.3, 14.2.

**Fluorovinyl benzene**

To a solution of aldehyde 18a (15 mg, 0.1 mmol) in cyclohexane (1.3 mL) was added Pd(OAc)$_2$ (1.8 mg, 0.008 mmol) and 4Å MS (30 mg). The resulting mixture was stirred at 140 °C for 72 h in a sealed tube. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford fluoroalkene 24 (9.3 mg, 76%). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.57-7.55 (m, 2H), 7.38-7.37 (m, 3H), 5.04 (dd, $J_1 = 49.7$ Hz, $J_2 = 3.3$ Hz, 1H), 4.86 (dd, $J_1 = 18.0$ Hz, $J_2 = 3.3$ Hz, 1H).

**(Z)-3-fluoro-1-nitro-3-phenylprop-2-en-1-ol**

To a solution of aldehyde 18a (20 mg, 0.134 mmol) in THF (1 mL) was added CH$_3$NO$_2$ (22.8 μL, 0.402 mmol) and compound 26 (25.2 μL, 0.201 mmol), sequentially.
The reaction mixture was stirred at rt for 3 h, and then poured into ice-water. The mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford product 27 in 83% yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.55-7.52 (m, 2H), 7.41-7.39 (m, 3H), 5.56-5.41 (m, 2H), 4.57 (d, $J = 5.4$ Hz, 2H), 2.71 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 160.6, 157.2, 130.6, 130.2, 129.9, 128.5, 124.6, 124.5, 102.5, 102.3, 79.1, 63.4, 63.3.

(\(E\))-5-benzyl-2,2,3-trimethyl-1-(3-oxo-3-phenylprop-1-en-1-yl)imidazolidin-4-one

To a solution of aldehyde 18a (15 mg, 0.1 mmol) in CHCl$_3$ (0.5 mL) was added pyridine (24 $\mu$L, 0.3 mmol) and compound 28 (30.6 mg, 0.12 mmol). The reaction mixture was stirred at rt for 16 h, and then diluted in EtOAc. The mixture was washed with 5% HCl aqueous solution, water and brine, sequentially. The organic layer was dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford product 29 in a quantitative yield. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.98-7.95 (m, 2H), 7.89 (d, $J = 12.6$ Hz, 1H), 7.53-7.44 (m, 3H), 7.24-7.19 (m, 3H), 7.12-7.09 (m, 2H), 6.10 (d, $J = 12.6$ Hz, 1H), 4.43 (d, $J = 3.9$ Hz, 1H), 3.49 (dd, $J_1 = 14.0$ Hz, $J_2 = 5.3$ Hz, 1H), 3.28 (dd, $J_1 = 14.0$ Hz, $J_2 = 2.0$ Hz, 1H), 3.28 (dd, $J_1 = 14.0$ Hz, $J_2 = 2.0$ Hz, 1H), 3.28 (dd, $J_1 = 14.0$ Hz, $J_2 = 2.0$ Hz, 1H).
Hz, 1H), 2.72 (s, 3H), 1.45 (s, 3H), 0.57 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 188.5, 167.5, 144.0, 139.7, 135.2, 131.7, 130.2, 128.4, 128.3, 127.7, 127.3, 96.0, 79.6, 61.0, 33.3, 27.4, 24.9, 24.8. MS (ESI$^+$) m/z (M+H)$^+$ calcd for C$_{22}$H$_{25}$N$_2$O$_2$ $^+$ 349.1911, found 349.1920.

3.6.3.2 Reactions Based on C=C bond of 18a

35

TBSCI, imidazole
yield quant.

N$_2$O$_2$OEt 36

Rh$_2$(OAc)$_4$
DCM, reflux, 5 h
yield 93%, dr > 10 : 1

37

Ti(OiPr)$_4$ 1 eq
(D)-DET 1.4 eq
TBHP 2 eq
4A MS
DCM, 0 °C, 5 h
yield 75%, 34% ee

22

O

F

O

Et$_2$Zn (3 equiv.)
CH$_2$I (6 equiv.)
Et$_2$O (6 equiv.)
DCM, 0 °C, 12 h
yield 82%, 42% ee

34

F

O

32

(3-Fluoro-3-phenyloxiran-2-yl)methanol
To a mixture of 4Å MS (10 beads) and (D)-DET (48 µL, 0.28 mmol) in anhydrous DCM (1.5 mL) at -20 °C were successively added Ti(i-PrO)$_4$ (60 µL, 0.2 mmol) and TBHP (72 µL, 0.4 mmol). The mixture was stirred at this temperature for 0.5 h. A solution of alcohol 22 (30 mg, 0.2 mmol) in anhydrous DCM (0.5 mL) was then added to the reaction mixture. After stirring at 0 °C for 5 h, the mixture was hydrolyzed with a solution of FeSO$_4$ (1 g) and L-tartaric acid (0.3 g) in water (30 mL). The biphasic system was stirred during 20 min, extracted with EtOAc. The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford epoxide 32 (24.9 mg, 75% yield, 34% ee). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.44 (s, 5H), 4.10-4.04 (m, 2H), 3.38-3.34 (m, 1H), 1.87 (br, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 133.2, 132.7, 129.7, 128.5, 125.5, 125.4, 98.2, 94.7, 64.6, 64.3, 60.1, 60.0. $^{19}$F NMR (282 MHz, CDCl$_3$): δ -148.37.

![Chemical structure of 34](image)

(2-Fluoro-2-phenylcyclopropyl)methanol

Et$_2$Zn (1M in hexanes, 300 µL, 0.3 mmol) and CH$_2$I$_2$ (47.7 µL, 0.6 mmol) were successively added to a mixture of anhydrous DCM (0.8 mL) and Et$_2$O (62.2 µL, 0.6 mmol) at -20 °C. The resulting mixture was stirred at this temperature for 10 min. A solution of boron ligand 33 (32 mg, 0.12 mmol) in anhydrous DCM (0.1 mL) was then added. The resulting mixture was stirred at this temperature for 5 min. A solution of
alcohol 22 (15 mg, 0.1 mmol) in anhydrous DCM (0.1 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to 0 °C and stirred for 12 h at this temperature. The reaction was quenched by adding a saturated NH₄Cl aqueous solution. The mixture was extracted with DCM. The combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford flurorcyclopropane 34 (13.4 mg, 82% yield, 42% ee). 

\[
\text{^1H NMR (300 MHz, CDCl₃): } \delta 7.40-7.35 \text{ (m, 2H), 7.32-7.28} \text{ (m, 3H), 4.06 (ddd, } J_1 = 11.7 \text{ Hz, } J_2 = 5.9 \text{ Hz, } J_3 = 1.2 \text{ Hz, 1H), 3.86-3.78} \text{ (m, 1H), 1.72-1.63} \text{ (m, 2H), 1.43-1.26} \text{ (m, 2H).}
\]

\[
\text{^13C NMR (75 MHz, CDCl₃): } \delta 139.1, 138.8, 128.3, 127.5, 124.2, 124.1, 82.8, 80.0, 61.6, 61.5, 28.0, 17.8, 17.9, 17.7.
\]

\[
\text{^19F NMR (282 MHz, CDCl₃): } \delta -191.9.
\]

(Z)-tert-butyl((3-fluoro-3-phenylallyl)oxy)dimethylsilane

To a solution of alcohol 22 (30 mg, 0.2 mmol) in DCM was added imidazole (20 mg, 0.3 mmol) and TBSCl (45 mg, 0.3 mmol), successively. After stirred at rt for 2 h, the reaction mixture was poured into ice-water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford protected product 35 in a quantitative yield.

\[
\text{^1H NMR (300 MHz, CDCl₃): } \delta 7.55-7.51 \text{ (m, 2H),}
\]

\[
\text{7.40-7.35} \text{ (m, 2H), 7.32-7.28} \text{ (m, 3H), 4.06 (ddd, } J_1 = 11.7 \text{ Hz, } J_2 = 5.9 \text{ Hz, } J_3 = 1.2 \text{ Hz, 1H), 3.86-3.78} \text{ (m, 1H), 1.72-1.63} \text{ (m, 2H), 1.43-1.26} \text{ (m, 2H).}
\]

\[
\text{^13C NMR (75 MHz, CDCl₃): } \delta 139.1, 138.8, 128.3, 127.5, 124.2, 124.1, 82.8, 80.0, 61.6, 61.5, 28.0, 17.8, 17.9, 17.7.
\]

\[
\text{^19F NMR (282 MHz, CDCl₃): } \delta -191.9.
\]
7.41-7.34 (m, 3H), 5.59 (dt, $J_1 = 36.9$ Hz, $J_2 = 6.8$ Hz, 1H), 4.50 (dd, $J_1 = 6.8$ Hz, $J_2 = 2.3$ Hz, 2H), 0.94 (s, 9H), 0.13 (s, 6H).

**Ethyl 3-(((tert-butyldimethylsilyl)oxy)methyl)-2-fluoro-2-phenylcyclopropane carboxylate**

To a mixture of compound 35 (25 mg, 0.094 mmol) and Rh$_2$(OAc)$_4$ (4 mg, 0.009 mmol) in anhydrous DCM (6 mL) at 40 °C was slowly added a solution of diazo-compound 36 (70 μL, 0.564 mmol) in anhydrous DCM (3 mL) via a syringe pump during 2 h. The resulting mixture was refluxed for another 5h. The mixture was then cooled to rt, washed successively with saturated NaHCO$_3$ aqueous solution, water and brine, dried over anhydrous Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford fluorocyclopropane 37 (30.8 mg, 93% yield, dr > 10:1). $^1$H NMR (300 MHz, CDCl$_3$): δ 7.39-7.35 (m, 5H), 4.39-4.25 (m, 2H), 4.18 (dd, $J_1 = 14.1$ Hz, $J_2 = 7.2$ Hz, 2H), 2.22 (dd, $J_1 = 10.8$ Hz, $J_2 = 5.7$ Hz, 1H), 2.09-2.01 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 167.0, 128.6, 128.4, 125.2, 125.1, 60.8, 56.4, 56.2, 32.2, 29.6, 29.5, 25.9, 18.3, 14.2, -5.3. $^{19}$F NMR (282 MHz, CDCl$_3$): δ -195.9.
2-Fluoro-3-(hydroxymethyl)-2-phenylcyclopropanecarboxylic acid

TBAF (1M in THF, 150 μL, 0.15 mmol) was slowly added to a solution of compound 37 (25 mg, 0.075 mmol) in THF (1 mL) at 0 °C. The reaction solution was stirred at rt for 17 h, and then poured into ice-water. The mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford deprotected product 38 (5.9 mg, 38% yield). ¹H NMR (500 MHz, CDCl₃): δ 7.44-7.40 (m, 3H), 7.31-7.29 (m, 2H), 4.65 (d, J = 1.5 Hz, 2H), 2.81-2.78 (m, 1H), 2.75 (d, J = 4.5 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 170.8, 135.0, 134.7, 128.8, 128.7, 124.4, 124.3, 78.3, 77.1, 65.5, 65.4, 32.5, 32.3, 31.0, 30.8.
3.7 References


# List of Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
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<td>camphor-10-sulfonic acid</td>
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