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

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by

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

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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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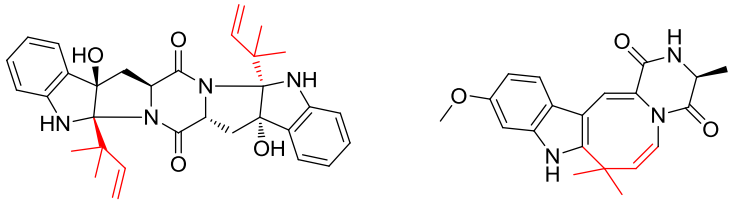
1. Aza-Claisen Rearrangement Involved Syntheses of 2-Alkylidene Substituted Indolines

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 ^{o}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-*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-*tert*-prenylation of indoles, remains to be developed.



fellutanine D (**1**) cycloechinulin (**2**)

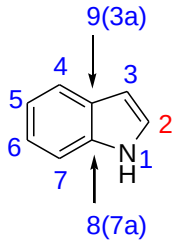
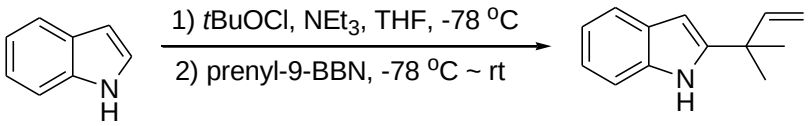
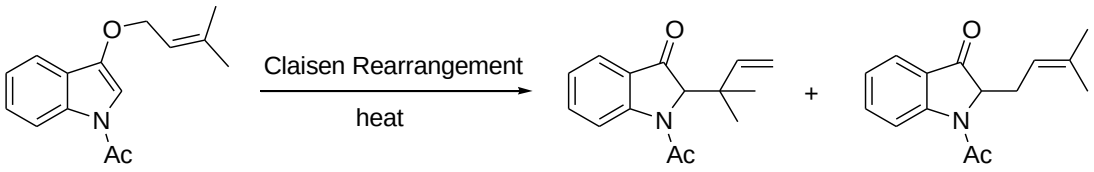


Figure 1.1.1 Numbering of the indole system.



Scheme 1.1.1 Nucleophilic tert-prenylation.

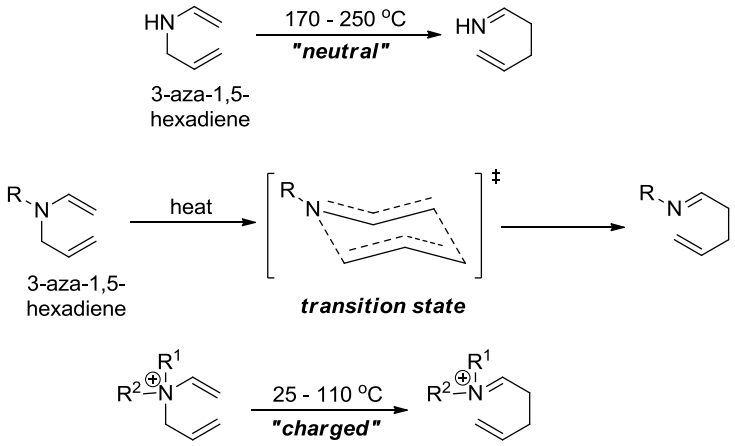


Scheme 1.1.2 Claisen Rearrangement.

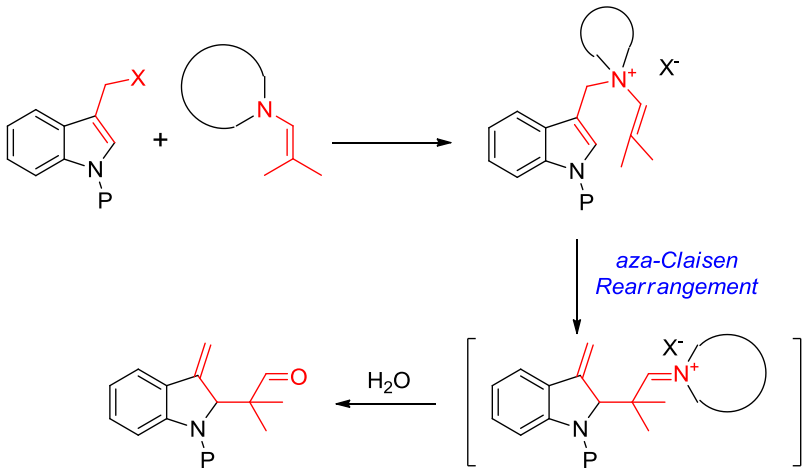
1.2 Research Design

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).[8] 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

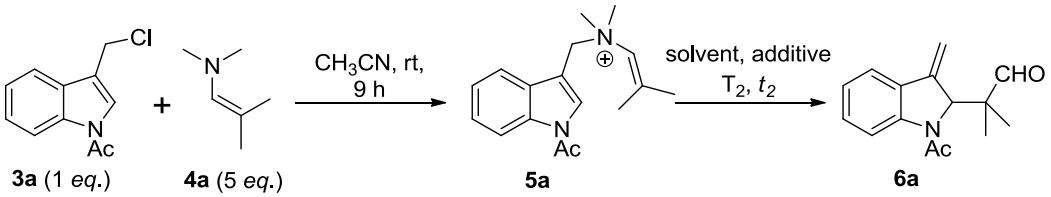


Scheme 1.2.2 Strategy in this work (P = protecting group, X = halide substituent).

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]



3a (1 *eq.*) **4a** (5 *eq.*) **5a** **6a**

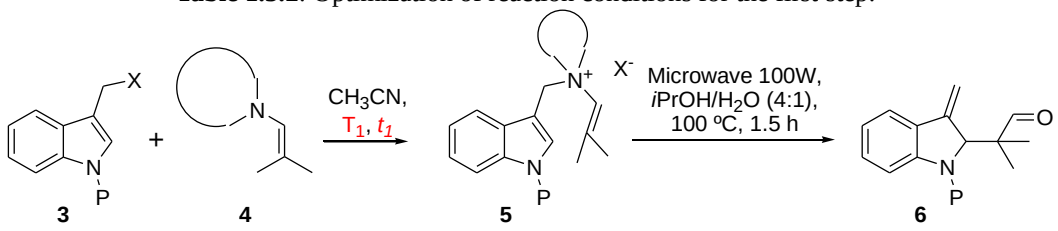
Entry	Solvent	Additive (2 *eq.*)	T_2 (°C)	t_2 (h)	Yield (%) (for 2 steps)
1	H_2O	-	100 (no MW)	3	22
2	H_2O	-	100 (no MW)	12	17
3	H_2O	-	100[b]	0.8	26
4	EtOH/H_2O=1:2	-	100[b]	0.8	31
5	EtOH/H_2O=2:1	-	100[b]	0.8	36
6	EtOH/H_2O=4:1	-	100[b]	0.8	39
7	EtOH	-	100[b]	0.8	<5
8	EtOH/H_2O=4:1	-	100[b]	1.5	48
9	EtOH/H_2O=4:1	-	100[b]	2	43
10	EtOH/H_2O=4:1	-	100[b]	2.5	40
11	DMF/H_2O=4:1	-	100[b]	1.5	41
12	CH_3CN/H_2O=4:1	-	100[b]	1.5	44
13	*i*PrOH/H_2O=4:1	-	100[b]	1.5	51
14	*t*BuOH/H_2O=4:1	-	100[b]	1.5	39
15	*i*PrOH/H_2O=4:1	PhCOOH	100[b]	1.5	43
16	*i*PrOH/H_2O=4:1	Bu_4NBr	100[b]	1.5	38
17	*i*PrOH/H_2O=4:1	4Å MS	100[b]	1.5	40

[a] The reactions were carried out on a 0.05-mmol scale of **3a** and monitored by appearance of **6a** by TLC and ^{1}HNMR 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 ^{o}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_2O = 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]



Entry	3	4	T_1 (°C)	t_1	Yield (%, for 2 steps)
1	**3a** (X = Cl, P = Ac)	**4a** (N,N-dimethyl-)	rt	9 h	51
2	**3b** (X = Cl, P = Ms)	**4a**	rt	9 h	55
3	**3c** (X = Cl, P = Boc)	**4a**	rt	9 h	35
4	**3d** (X = Cl, P = Tf)	**4a**	rt	9 h	No desired product
5	**3e** (X = Br, P = Ms)	**4a**	rt	2 h	45
6	**3e**	**4a**	rt	1 h	67
7	**3e**	**4a**	rt	0.5 h	58[b]
8	**3e**	**4b** (pyrrolidin-1-yl)	rt	0.5 h	67
9	**3e**	**4b**	rt	15 min	72
10	**3e**	**4b**	rt	12 min	77
11	**3e**	**4b**	rt	10 min	73
12	**3e**	**4b**	rt	5 min	56
13	**3e**	**4b**	50	12 min	58
14	**3e**	**4b**	0	12 min	33

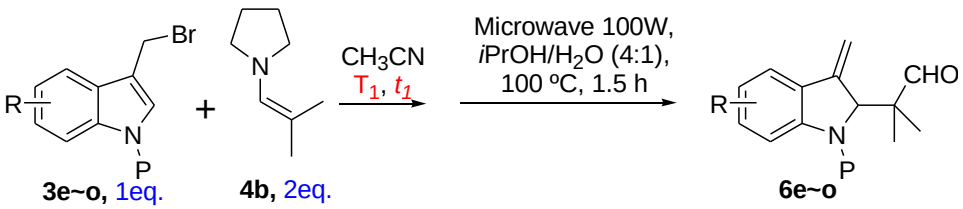
[a] The reactions were carried out on a 0.05-mmol scale of **3** and monitored by appearance of **6** by TLC and ^{1}HNMR spectroscopy. [b] Some of **3e** remained unreacted.

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.

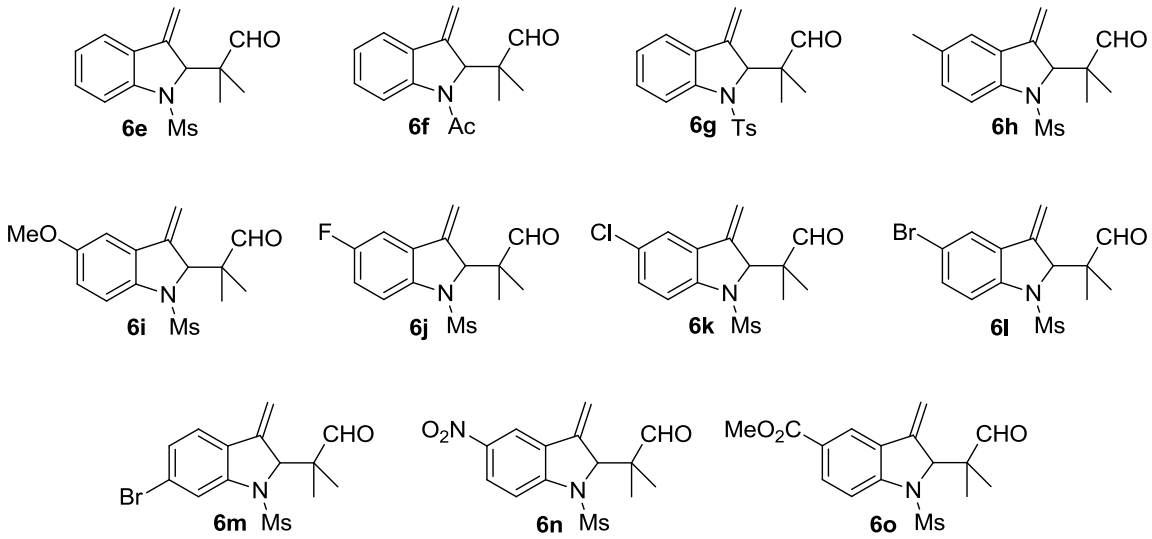
Table 1.3.3: Substrate scope of indole bromides.[a]



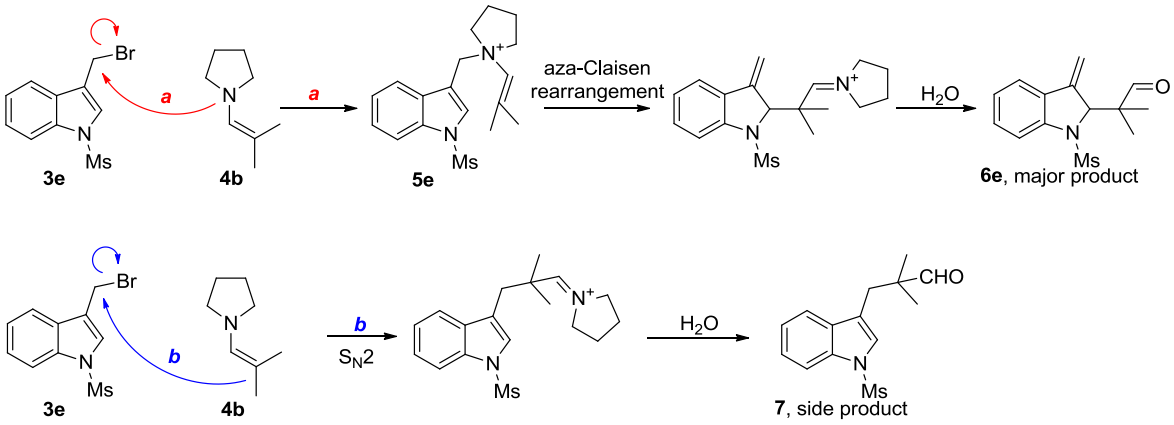
Entry	3	R	P	T_1 (°C)	t_1 (min)	6	Yield (%, for two steps)
1	**3e**	-	Ms	rt	12	**6e**	77
2	**3f**	-	Ac	rt	15	**6f**	37
3	**3g**	-	Ts	rt	20	**6g**	48
4	**3h**	5-CH_3	Ms	rt	15	**6h**	71
5	**3i**	5-OCH_3	Ms	rt	5	**6i**	73
6	**3j**	5-F	Ms	rt	45	**6j**	72
7	**3k**	5-Cl	Ms	50	15	**6k**	66
8	**3l**	5-Br	Ms	50	15	**6l**	64
9	**3m**	6-Br	Ms	rt	35	**6m**	66
10	**3n**	5-NO_2	Ms	rt	80	**6n**	66

11	**3o**	5-CO_2Me	Ms	50	15	**6o**	85

[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.



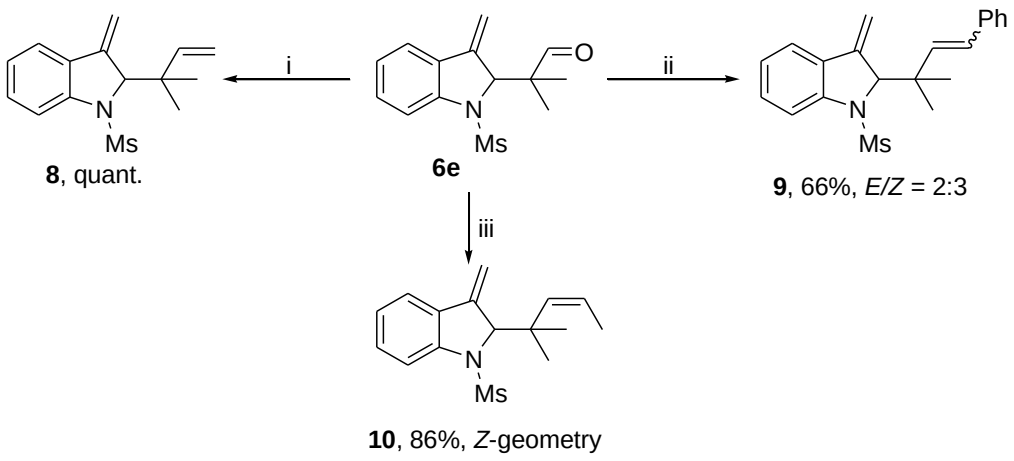
Although the yields of the two-step reactions are high in most cases, we observed a trace amount of compound **7** as a side product. We reasoned that the most probable mechanism for generation of compound **7** was S_N2 reaction of indole bromide **3e** (Scheme 1.3.1).



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

1.4 Derivatization

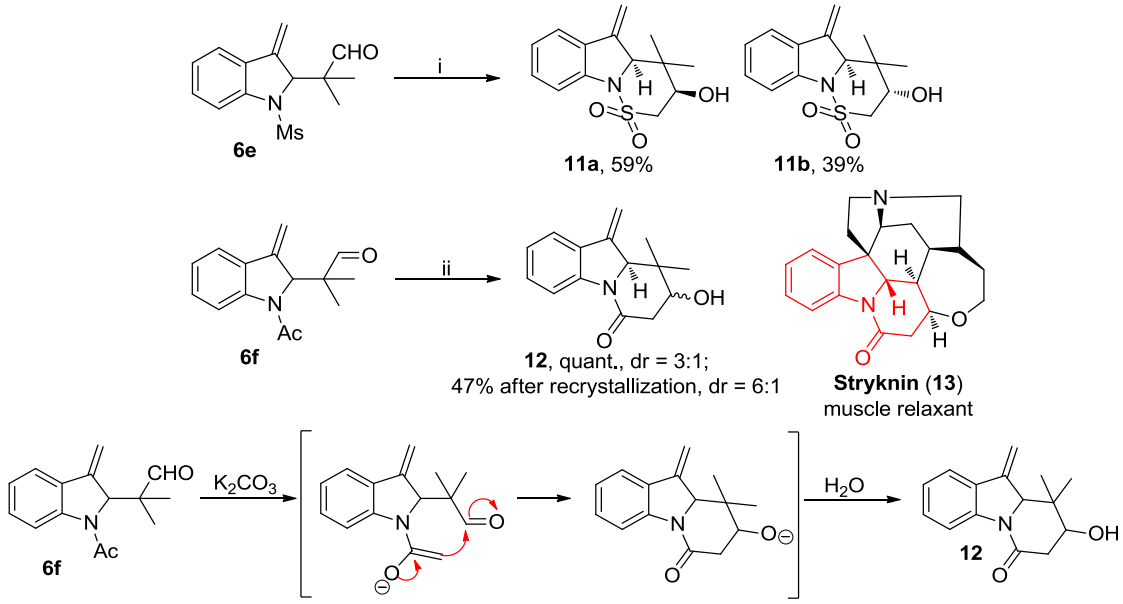
The second phase of this work was directed towards exploring the utility of these new building blocks **6**. One of our major goals for this work is to introduce a reverse prenyl group at indolyl C2-position. In order to achieve this goal, compound **6e** was treated with methyltriphenylphosphonium bromide 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) Ph_3PCH_2Br, n-BuLi, THF, 0 ^oC - rt; (ii) Ph_3PCH_2PhBr, n-BuLi, THF, 0 ^oC - rt; (iii) $Ph_3PCH_2CH_3Br$, n-BuLi, THF, 0 ^oC – rt.

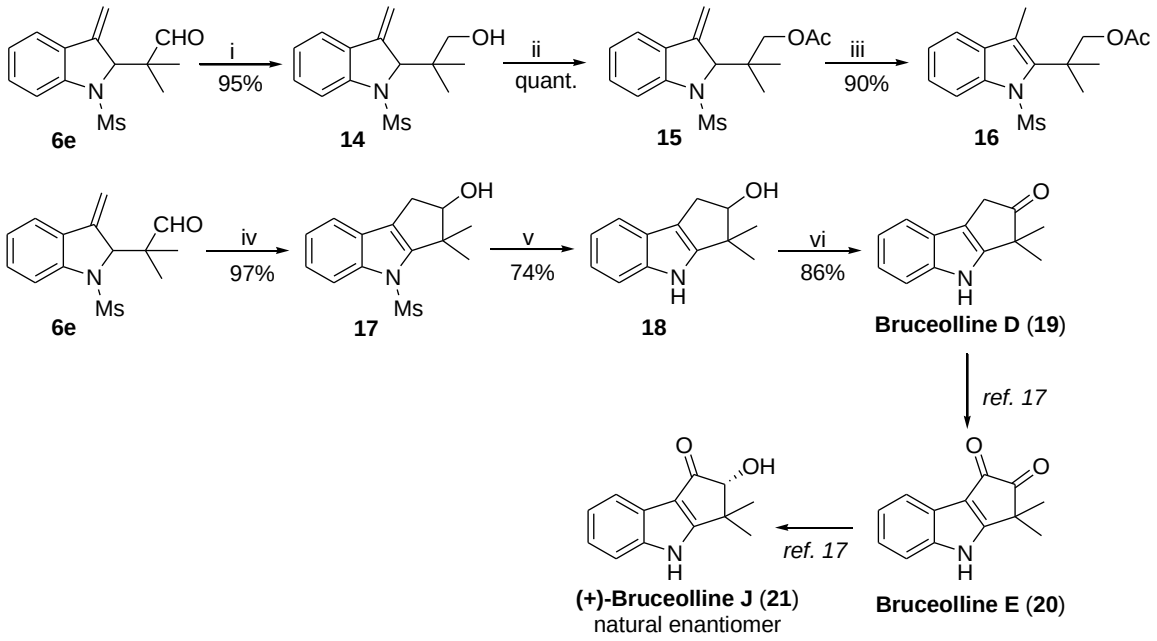
Interestingly, indoline-fused sultams (**11a** and **11b**) were generated when compound **6e** was treated with lithium hydroxide (Scheme 1.4.2). It is noted that sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties.[10] A number 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 I[14] and MMP-2[15]. In addition, tricyclic lactam **12** was obtained quantitatively from acetyl protected indoline **6f** by treatment with

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[16], 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_2CO_3, MeOH, 50 ^oC.

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.[17]



Scheme 1.4.3 Syntheses of re-aromatised indole **16** and bruceolline D (**19**). *Reagents and conditions*: (i) $NaBH_4$, MeOH, 0 ^oC; (ii) Ac_2O, DMAP, CH_2Cl_2, 0 ^oC; (iii) $TiCl_4$, CH_2Cl_2, rt; (iv) $TiCl_4$, CH_2Cl_2, rt; (v) MeONa, MeOH, reflux; (vi) IBX, DMSO, rt.

1.5 Conclusions

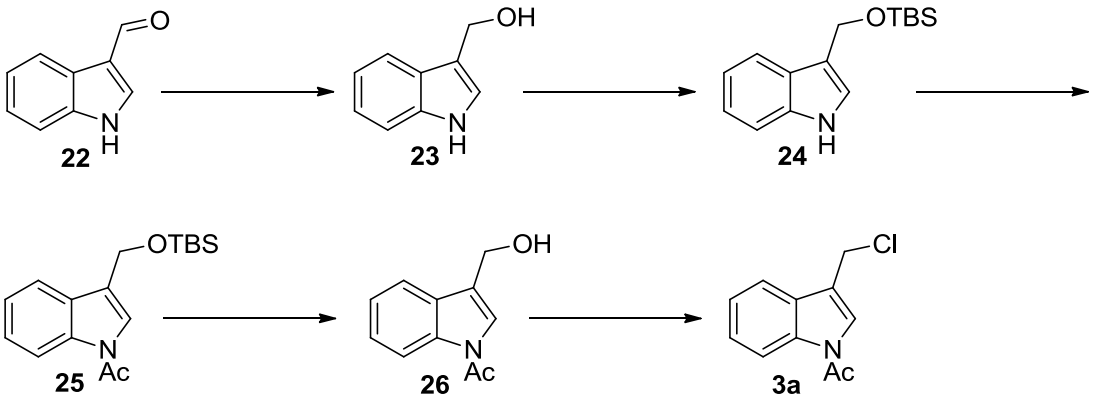
In summary, we have developed a novel aza-Claisen rearrangement involved a two-step reaction of indole bromides (**3**) with enamine (**4b**) as an effective method for the generation of 2-alkylidene substituted indolines (**6**). These products can be conveniently elaborated to synthesize new molecules,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

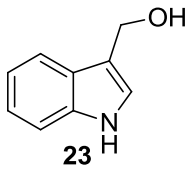
1.6 Experimental Section

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. $CDCl_3$ (δ = 7.26 and 77.0 for ^{1}H and $^{13}CNMR$ spectra respectively) and DMSO-d6 (δ = 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

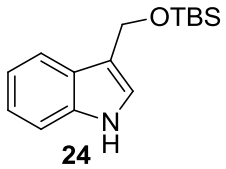




23

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

To a solution of aldehyde **22** (2.90 g, 20 mmol) in MeOH (20 mL) was added $NaBH_4$ (756 mg, 20 mmol) in some portions slowly within 30 min at 0 ℃. The reaction was continuted to stir at 0 ℃ for 30 min. Brine 30 mL was added and extrated with EtOAc for three times. The organic layers were combined and dried over anhydrous Na_2SO_4 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%. ^{1}H NMR (300 MHz, $CDCl_3$): 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).

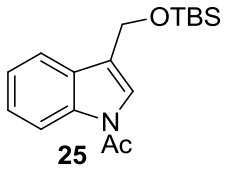


24

3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1*H*-indole

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

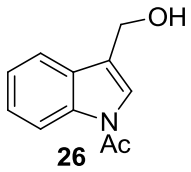
layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was submitted to chromatography to give the desired product **24** (1.37 g, yield: 100%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (br, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.23-6.97 (m, 3H), 4.95 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H).



25

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

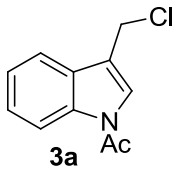
To a solution of compound **24** (1.37 g, 5.2 mmol) and Et_3N (2.1 g, 20.8 mmol) in CH_2Cl_2 (5 mL) was added Ac_2O (2.12 g, 20.8 mmol). The reaction was refluxed for 15 h. Solvent and excess reactants were removed under reduced pressure. The residue was submitted to chromatography to give the desired product **25** (1.40 g, yield: 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 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).



26

1-(3-(Hydroxymethyl)-1*H*-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 $NaHCO_3$ 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 Na_2SO_4 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). ^{1}H NMR (300 MHz, $CDCl_3$): 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).

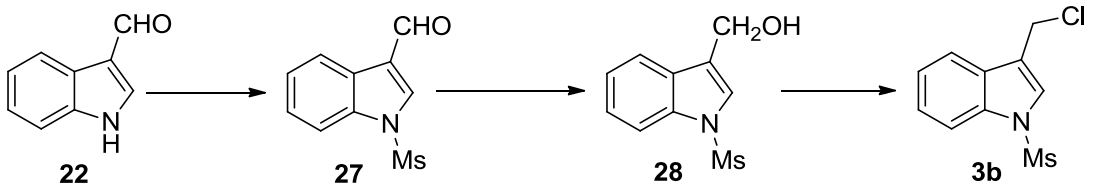


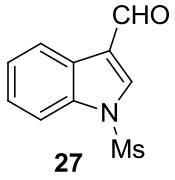
3a

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

To a solution of compound **26** (720 mg, 3.8 mmol) and Et_3N (768 mg, 7.6 mmol) in CH_2Cl_2 (25 mL) was added MsCl (545 mg, 4.7 mmol) within 15 min at 0 ℃. 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%). ^{1}H NMR (300 MHz, $CDCl_3$): 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).

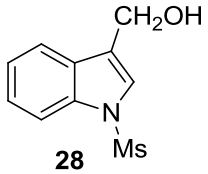
1.6.1.2 Procedures for the preparation of substrates 3b





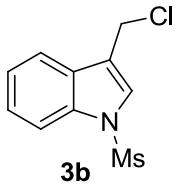
1-(Methylsulfonyl)-1*H*-indole-3-carbaldehyde

To a solution of aldehyde **22** (1.45 g, 10 mmol) and Et_3N (4.05 mg, 5.6 mL, 40 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ℃ 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_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product **27** (1.83 g, yield 82%). ^{1}H NMR (500 MHz, $CDCl_3$): 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)-1*H*-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, $CDCl_3$): 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).

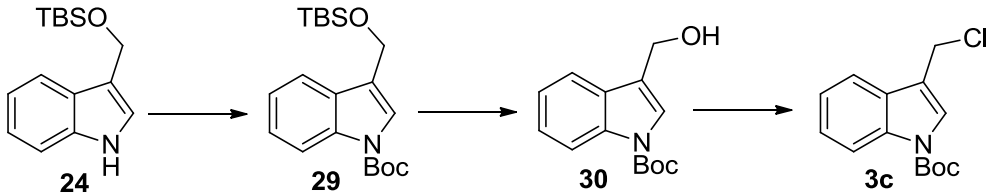


3b

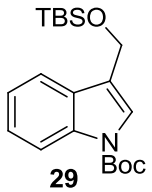
3-(Chloromethyl)-1-(methylsulfonyl)-1*H*-indole

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, CDCl3): δ 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



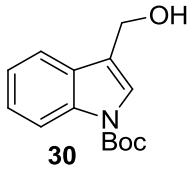
24 **29** **30** **3c**



29

***tert*-Butyl 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-indole-1-carboxylate**

To a solution of compound **24** (261 mg, 1.0 mmol) and DMAP (24 mg, 0.2 mmol) in CH_3CN (5 mL) was added $(Boc)_2O$ (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_2SO_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, 122.9, 122.4, 121.0, 119.4, 115.2, 83.3, 58.0, 28.1, 27.4, 25.9, 18.4, -5.3.

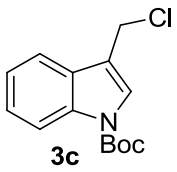


30

***tert*-Butyl 3-(hydroxymethyl)-1*H*-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).

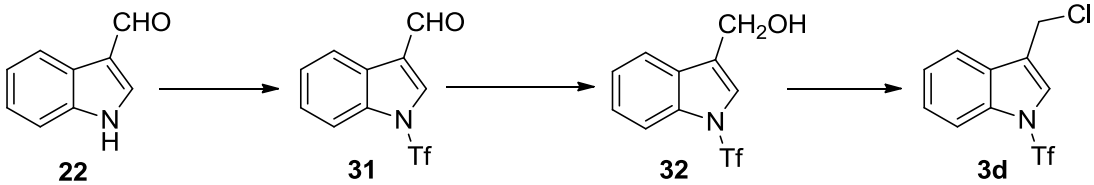


3c

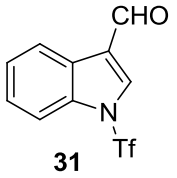
***tert*-Butyl 3-(chloromethyl)-1*H*-indole-1-carboxylate**

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



22 **31** **32** **3d**

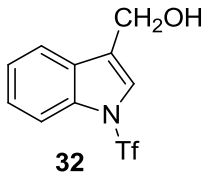


31

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

To a solution of aldehyde **22** (290 mg, 2 mmol), Et_3N (810 mg, 1.1 mL, 8 mmol) and DMAP (244 mg, 2 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ℃ was added Tf_2O (1 mL,

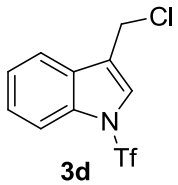
6 mmol) dropwise. After addition, the reaction was stirred for 30 min at 0 ℃. Ice-water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product **31** (360 mg, yield 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.50 (m, 2H).



32

(1-((Trifluoromethyl)sulfonyl)-1*H*-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, $CDCl_3$): δ 7.91 (dd, J_1 = 7.1 Hz, J_2 = 1.7 Hz, 1H), 7.70 (m, 1H), 7.46-7.38 (m, 3H), 4.89 (d, *J* = 4.5 Hz, 2H), 1.72 (t, *J* = 4.5 Hz, 1H).



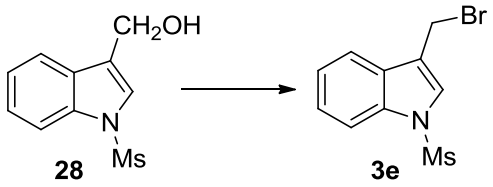
3d

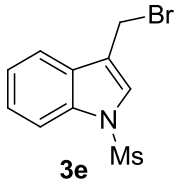
3-(Chloromethyl)-1-((trifluoromethyl)sulfonyl)-1*H*-indole

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



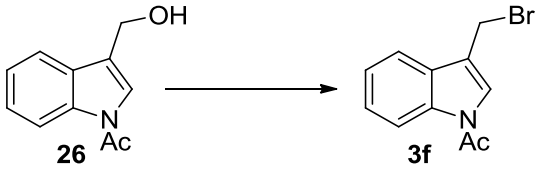


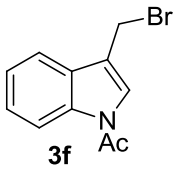
3-(Bromomethyl)-1-(methylsulfonyl)-1*H*-indole

To a solution of compound **28** (3.05 g, 13.5 mmol) in anhydrous CH_2Cl_2 (30 mL) was added PBr_3 (4.8 g, 1.7 mL, 17.6 mmol) at 0 ℃. 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_2SO_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,

$CDCl_3$): δ 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).

1.6.2.2 Procedures for the preparation of substrates 3f

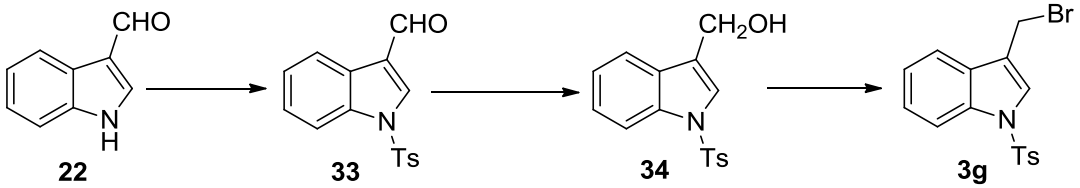


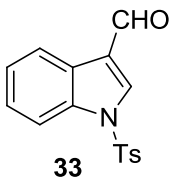


1-(3-(Bromomethyl)-1*H*-indol-1-yl)ethanone

The title compound was prepared in the same procedure as described above in the preparation of compound **3e** in 68% yield. ^{1}H 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).

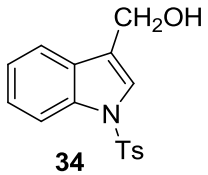
1.6.2.3 Procedures for the preparation of substrates 3g





1-Tosyl-1*H*-indole-3-carbaldehyde

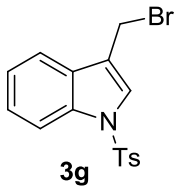
To a solution of aldehyde **22** (1.45 g, 10 mmol), Et_3N (2 g, 2.8 mL, 20 mmol) and DMAP (122 mg, 1 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 ℃ was added a solution of TsCl (2.86 g, 15 mmol) in anhydrous CH_2Cl_2 (10 mL) dropwise. After addition, the reaction was warmed to rt and stirred for 3.5 hours. 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_2SO_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, $CDCl_3$): δ 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).



34

(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, $CDCl_3$): δ 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).

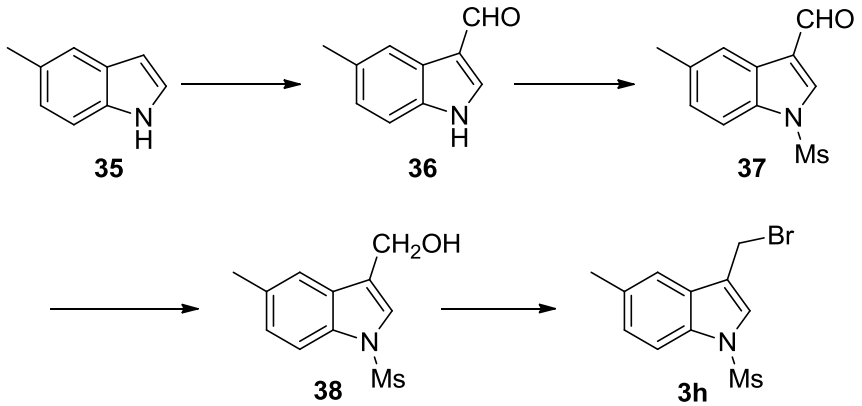


3g

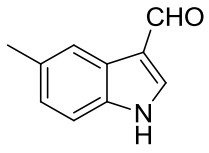
3-(Bromomethyl)-1-tosyl-1*H*-indole

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



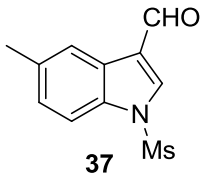
35 **36** **37** **38** **3h**



36

5-Methyl-1*H*-indole-3-carbaldehyde

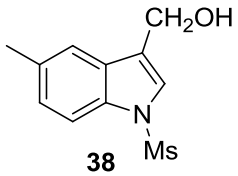
$POCl_3$ (103 μL, 1.1 mmol) was added dropwise to anhydrous DMF (472 μL) that was maintained at 10-20 ℃. The resulting mixture was stirred for 30 min and then chilled to 0 ℃. A solution of compound **35** (159 mg, 1 mmol) in anhydrous DMF (285 μL) was added. The ice bath was removed and the solution 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%). ^{1}H 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, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H), 2.49 (s, 3H).



37

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

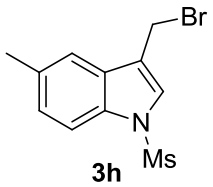
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 3.26 (s, 3H), 2.50 (s, 3H).



38

(5-Methyl-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).

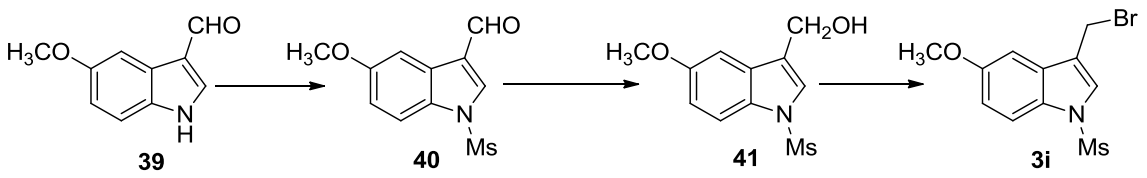


3h

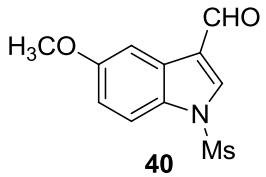
3-(Bromomethyl)-5-methyl-1-(methylsulfonyl)-1*H*-indole

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, $CDCl_3$): δ 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



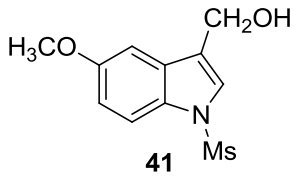
39 **40** **41** **3i**



40

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

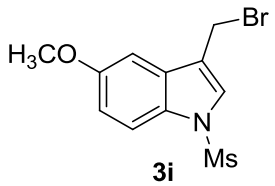
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.06 (s, 1H), 7.81-7.75 (m, 2H), 7.08 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 3.91 (s, 3H), 3.26 (s, 3H).



41

(5-Methoxy-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).

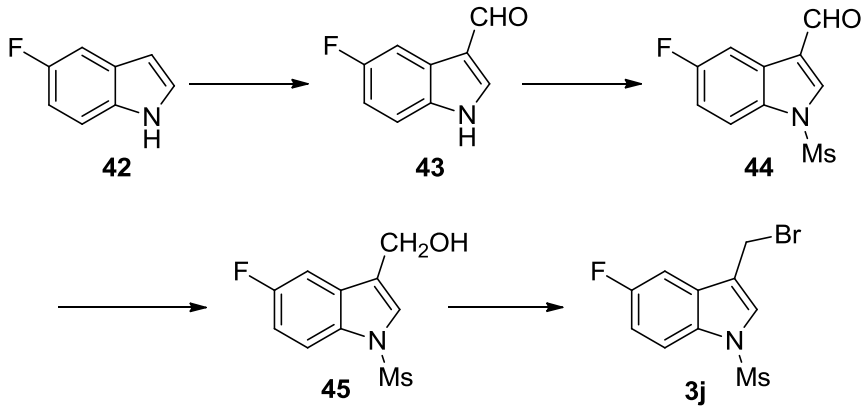


3i

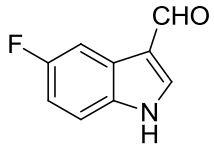
3-(Bromomethyl)-5-methoxy-1-(methylsulfonyl)-1*H*-indole

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, $CDCl_3$): δ 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



42 **43** **44** **45** **3j**

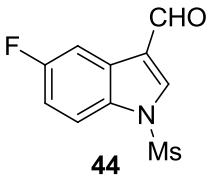


43

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

$POCl_3$ (1 mL, 11 mmol) was added dropwise to anhydrous DMF (5 mL) at 0 ℃. The resulting mixture was stirred for 30 min at rt and then chilled to 0 ℃. A solution of

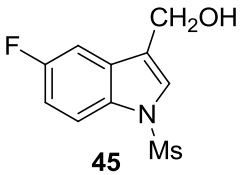
compound **42** (1.35 g, 10 mmol) in anhydrous DMF (1.4 mL) was added. The ice bath was removed and the solution was warmed to rt. After 3 hours, the reaction mixture was poured into ice, 6M NaOH aqueous solution was added until pH was strongly basic. The mixture was refluxed overnight and then cool 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, $CDCl_3$): δ 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).



44

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

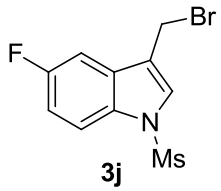
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 66% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.09 (s, 1H), 8.70 (s, 1H), 7.96-7.86 (m, 2H), 7.39 (td, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 1H), 3.71 (s, 3H).



45

(5-Fluoro-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).

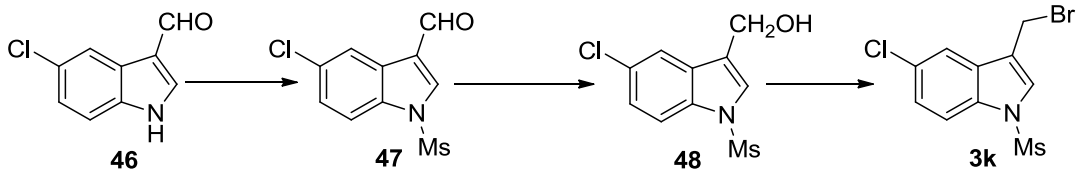


3j

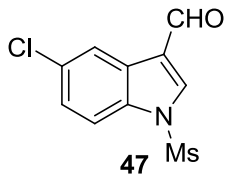
3-(Bromomethyl)-5-fluoro-1-(methylsulfonyl)-1*H*-indole

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, $CDCl_3$): δ 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



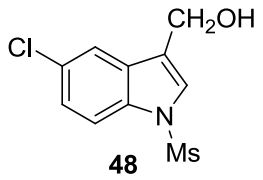
46 **47** **48** **3k**



47

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

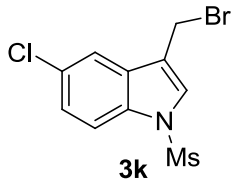
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.37 (s, 1H), 8.12 (s, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 3.29 (s, 3H).



48

(5-Chloro-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).

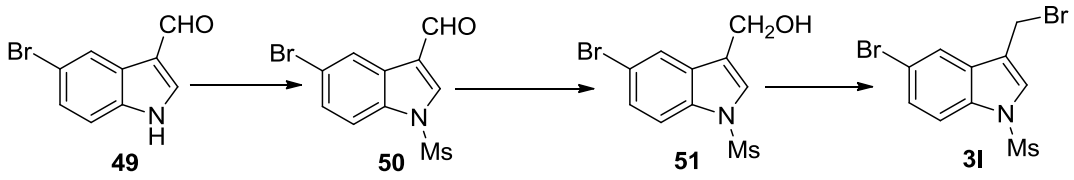


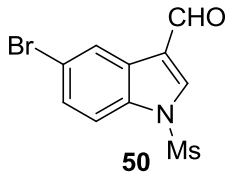
3k

3-(Bromomethyl)-5-chloro-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).

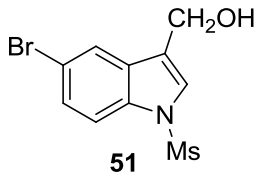
1.6.2.8 Procedures for the preparation of substrates 3l





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

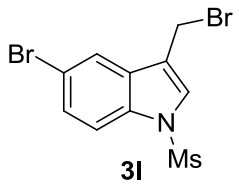
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.53 (s, 1H), 8.11 (s, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 3.29 (s, 3H).



(5-Bromo-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).

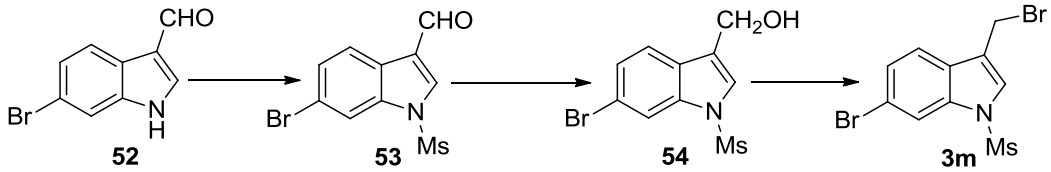


3l

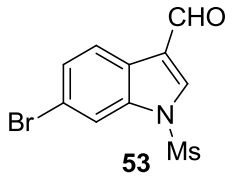
5-Bromo-3-(bromomethyl)-1-(methylsulfonyl)-1*H*-indole

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



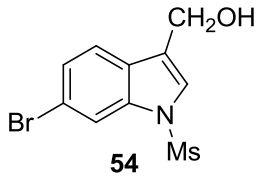
52 **53** **54** **3m**



53

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

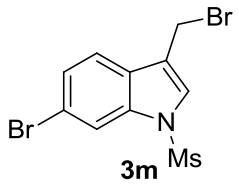
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 3.31 (s, 3H).



54

(6-Bromo-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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).



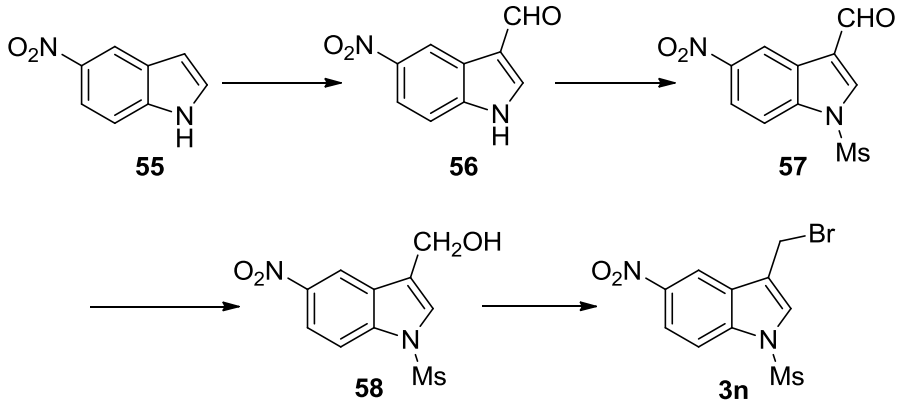
3m

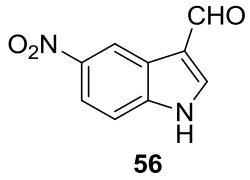
6-Bromo-3-(bromomethyl)-1-(methylsulfonyl)-1*H*-indole

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, $CDCl_3$): δ 8.09 (d, *J* = 1.5

Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.51 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 7.50 (s, 1H), 4.62 (d, J = 0.6 Hz, 2H), 3.17 (s, 3H).

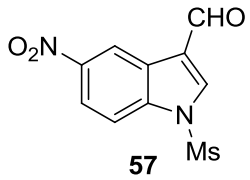
1.6.2.10 Procedures for the preparation of substrates 3n





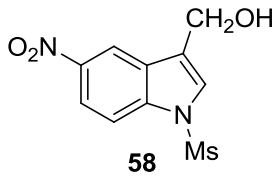
5-Nitro-1*H*-indole-3-carbaldehyde

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): δ 10.03 (s, 1H), 8.95 (d, J = 2.1 Hz, 1H), 8.58 (s, 1H), 8.16 (dd, J_1 = 9.0 Hz, J_2 = 2.1 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H).



1-(Methylsulfonyl)-5-nitro-1*H*-indole-3-carbaldehyde

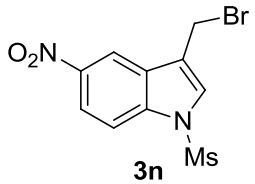
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 75% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.16 (s, 1H), 8.98 (d, J = 2.1 Hz, 1H), 8.90 (s, 1H), 8.38 (dd, J_1 = 9.3 Hz, J_2 = 2.1 Hz, 1H), 8.15 (d, J = 9.3 Hz, 1H), 3.82 (s, 3H).



58

(1-(Methylsulfonyl)-5-nitro-1*H*-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): δ 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).

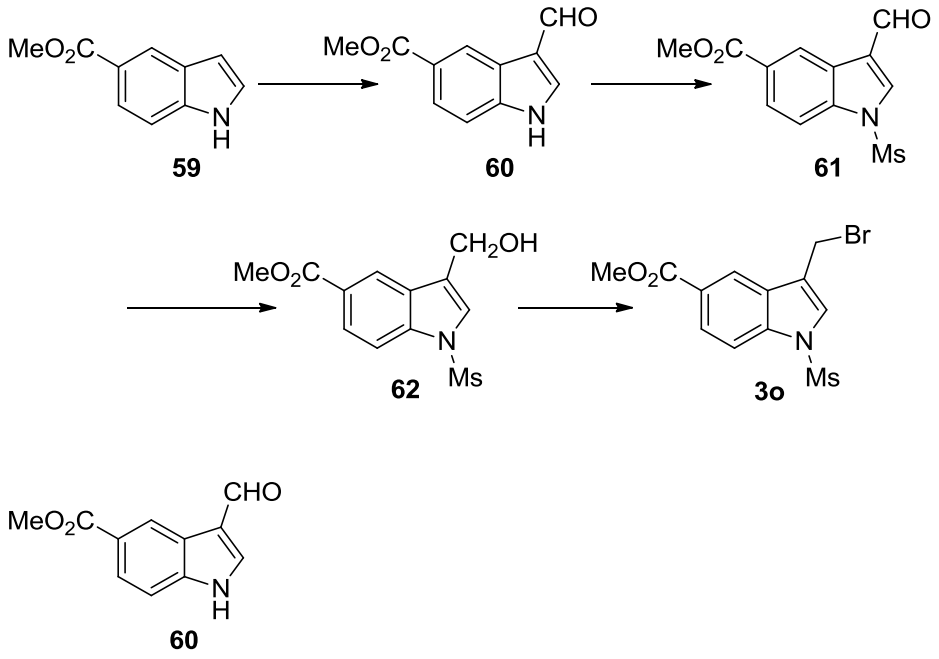


3n

3-(Bromomethyl)-1-(methylsulfonyl)-5-nitro-1*H*-indole

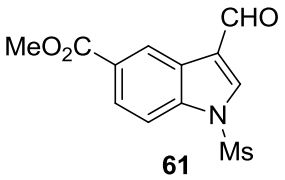
The title compound was prepared in the same procedure as described above in the preparation of compound **3e** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, J = 2.1 Hz, 1H), 8.33 (dd, J_1 = 9.0 Hz, J_2 = 2.1 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.70 (s, 1H), 4.67 (s, 2H), 3.25 (s, 3H).

1.6.2.11 Procedures for the preparation of substrates 3o



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

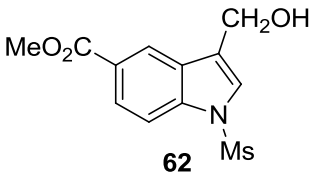
The title compound was prepared in the same procedure as described above in the preparation of compound **43** in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$ + 2 drops of MeOD-d_4): δ 10.00 (s, 1H), 8.95 (s, 1H), 7.97 (dd, J_1 = 8.7 Hz, J_2 = 1.5 Hz, 1H), 7.89 (s, 1H), 7.43 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H).



61

Methyl 3-formyl-1-(methylsulfonyl)-1*H*-indole-5-carboxylate

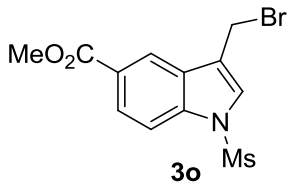
The title compound was prepared in the same procedure as described above in the preparation of compound **27** in 94% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.14 (s, 1H), 9.03 (s, 1H), 8.19 (dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1H), 8.18 (s, 1H), 7.95 (d, J = 8.7 Hz, 1H), 3.98 (s, 3H), 3.33 (s, 3H).



62

Methyl 3-(hydroxymethyl)-1-(methylsulfonyl)-1*H*-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).



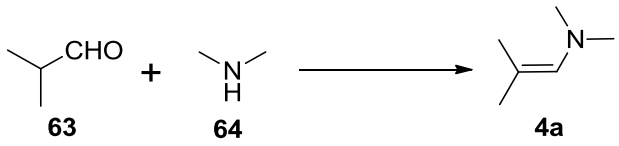
3o

Methyl 3-(bromomethyl)-1-(methylsulfonyl)-1*H*-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, $CDCl_3$): δ 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



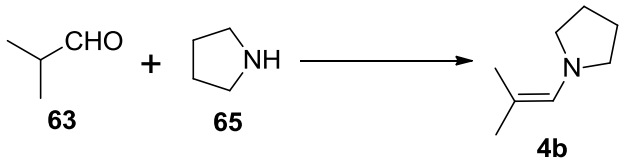
63 **64** **4a**

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

To a stirred solution of isobutyraldehyde **63** (7.2 g, 100 mmol) in Et_2O (50 mL) was added dimethylamine **64** (40% aq., 13.5 g, 120 mmol) slowly at 0 ℃, followed by the addition of anhydrous Na_2SO_4 (16 g) in one pot. The mixture was stirred vigorously for 20 min. The solution was transformed into another flask, anhydrous Na_2SO_4 (8 g) was added at 0 ℃ and the mixture was stirred vigorously for 10 min. Again, the solution was transformed into another flask, anhydrous Na_2SO_4 (5 g) was added at 0 ℃ 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, $CDCl_3$): δ 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

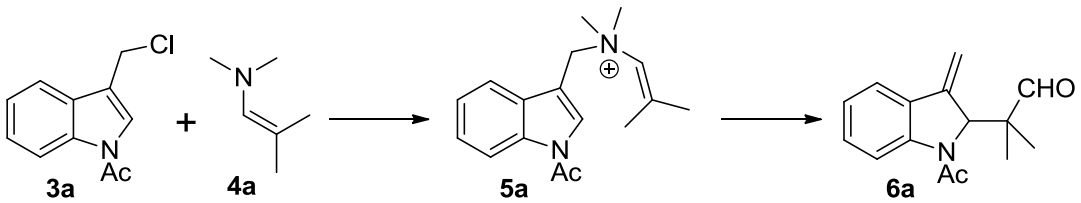


1-(2-Methylprop-1-en-1-yl)pyrrolidine (4b)

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 ℃/75 mmHg (92-106 ℃/115-118 mmHg[18]). ^{1}H NMR (300 MHz, $CDCl_3$): δ 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

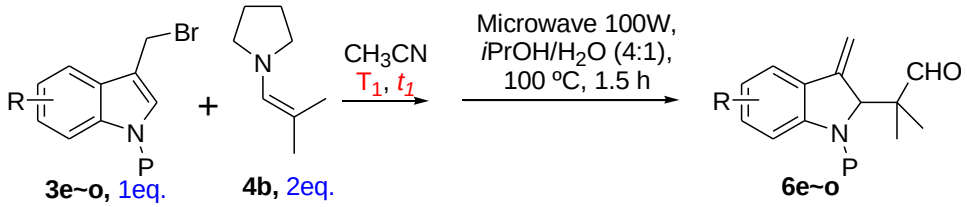
1.6.4.1 Typical Procedure for preparation of products 6 from indolyl chloride substrates



To a solution of compound **3a** (10.4 mg, 0.05 mmol) in anhydrous CH_3CN (0.2 mL) was added enamine **4a** (0.25 mmol, 5 eq.). The reaction was stirred at room temperature

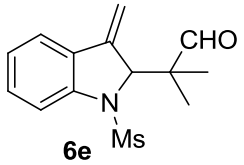
for 9 h before solvent and excess enamine **4a** were removed under reduced pressure. To the residue was added *i*-PrOH (1.2 mL) and H_2O (0.3 mL) and the reaction mixture was put into microwave condition (100 W, 100 ℃) for 90 min. The resulting mixture was added into brine (10 mL) and extracted with EtOAc for 3 times. The organic layers were combined and dried over anhydrous Na_2SO_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



General Procedure: To a solution of compound **3** (0.05 mmol, 1 eq.) in anhydrous CH_3CN (0.5 mL) was added enamine **4b** (0.1 mmol, 2 eq.). The reaction was stirred at room temperature or 50 ℃ for the time listed in Table 1.3.3. To the reaction mixture was added *i*-PrOH (1.2 mL) and H_2O (0.3 mL), and the resulting solution was put into microwave condition (100 W, 100 ℃). 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_2SO_4. The solvent was

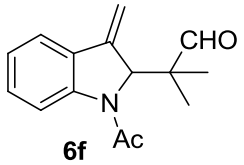
removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **6**.



6e

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 $C_{14}H_{18}NO_3S^+$ 280.1007, found 280.1008.

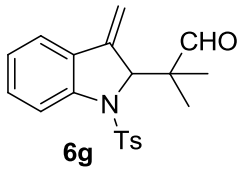


6f

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),

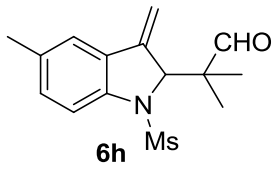
51.5 (C), 24.0 (CH_3), 18.2 (CH_3), 15.9 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{15}H_{18}NO_2^+$ 244.1338, found 244.1336.



6g

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

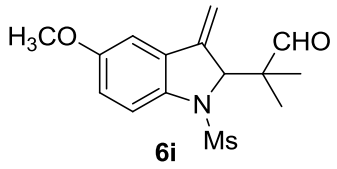
^1H NMR (300 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.28 (td, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.19 (dd, J_1 = 7.8 Hz, J_2 = 0.8 Hz, 1H), 7.08-7.05 (m, 3H), 5.29 (d, *J* = 1.5 Hz, 1H), 4.87 (d, *J* = 1.5 Hz, 1H), 4.86 (d, *J* = 4.5 Hz, 1H), 2.30 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 70.4 (CH), 51.7 (C), 21.5 (CH_3), 18.8 (CH_3), 17.7 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{20}H_{22}NO_3S^+$ 356.1320, found 356.1322.



6h

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

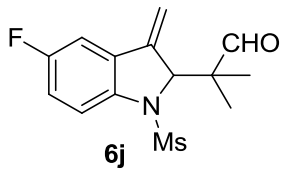
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.23 (s, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 5.62 (d, *J* = 1.2 Hz, 1H), 5.14 (s, 1H), 4.91 (s, 1H), 2.60 (s, 3H), 2.35 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8 (CH), 142.7 (C), 141.9 (C), 136.3 (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 $C_{15}H_{20}NO_3S^+$ 294.1164, found 294.1163.



6i

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

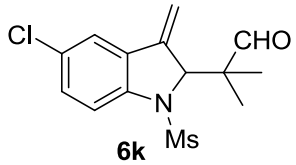
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 1.8 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.63 (d, *J* = 1.5 Hz, 1H), 5.17 (d, *J* = 0.9 Hz, 1H), 4.91 (t, *J* = 1.5 Hz, 1H), 3.82 (s, 3H), 2.59 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{15}H_{20}NO_4S^+$ 310.1113, found 356.1109.



6j

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

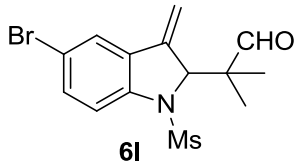
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.50 (dd, J_1 = 8.7 Hz, J_2 = 4.5 Hz, 1H), 7.11 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.02 (t, J = 8.7 Hz, 1H), 5.65 (d, J = 0.9 Hz, 1H), 5.24 (s, 1H), 4.97 (t, J = 1.5 Hz, 1H), 2.62 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5 (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 $C_{14}H_{17}FNO_3S^+$ 298.0913, found 298.0906.



6k

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

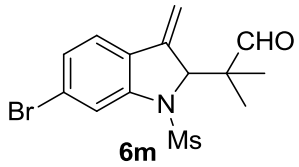
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 5.66 (d, J = 0.9 Hz, 1H), 5.24 (s, 1H), 4.98 (t, J = 1.5 Hz, 1H), 2.64 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4 (CH), 142.6 (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 $C_{14}H_{17}ClNO_3S^+$ 314.0618, found 314.0611.



6l

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

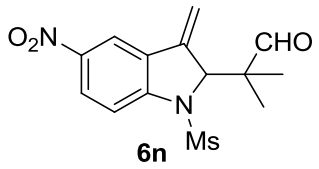
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.55 (s, 1H), 7.43 (s, 1H), 7.42 (s, 1H), 5.66 (d, *J* = 0.9 Hz, 1H), 5.23 (s, 1H), 4.97 (t, *J* = 1.5 Hz, 1H), 2.64 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4 (CH), 143.1 (C), 141.5 (C), 134.1 (C), 133.3 (CH), 124.0 (CH), 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 $C_{14}H_{17}BrNO_3S^+$ 358.0113, found 358.0114.



6m

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

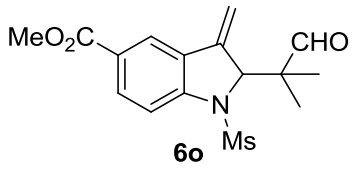
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.71 (d, *J* = 0.9 Hz, 1H), 7.35-7.28 (m, 2H), 5.65 (d, *J* = 0.9 Hz, 1H), 5.20 (s, 1H), 4.97 (s, 1H), 2.67 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.4 (CH), 145.1 (C), 141.6 (C), 131.1 (C), 129.5 (CH), 124.1 (C), 121.9 (CH), 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 $C_{14}H_{17}BrNO_3S^+$ 358.0113, found 358.0118.



6n

2-Methyl-2-(3-methylene-1-(methylsulfonyl)-5-nitroindolin-2-yl)propanal

^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{14}H_{17}N_2O_5S^+$ 325.0858, found 325.0864.



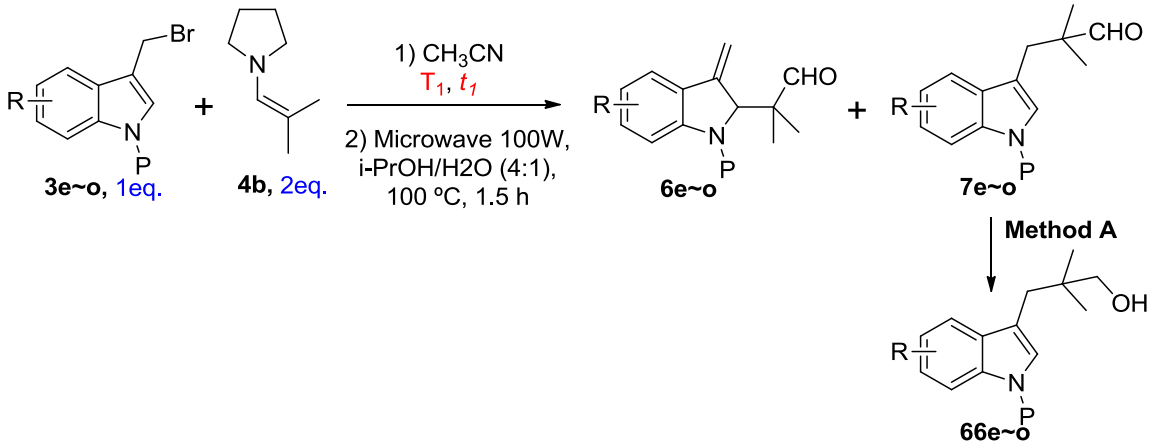
6o

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

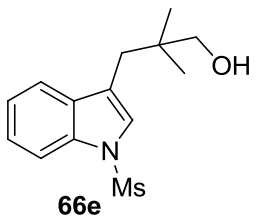
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.12 (d, J = 1.5 Hz, 1H), 8.02 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 5.77 (d, J = 1.2 Hz, 1H), 5.26 (s, 1H), 5.05 (s, 1H), 3.93 (s, 3H), 2.68 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (75 MHz,

$CDCl_3$): 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 (CH_2), 70.6 (CH), 52.4 (CH_3), 52.1 (C), 35.9 (CH_3), 18.5 (CH_3), 17.3 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{16}H_{20}NO_5S^+$ 338.1062, found 338.1062.

1.6.5 Preparation of side products 7 through aza-Claisen rearrangement

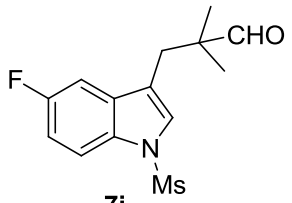


Method A: To a solution of aldehyde **7** (1 eq.) in MeOH was added $NaBH_4$ (1 eq.) in some portions slowly within 30 min at 0 ℃. The reaction was continuted to stir at 0 ℃ or rt for 30 min. Brine was added and extrated with EtOAc for three times. The organic layers were combined and dried over anhydrous Na_2SO_4 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)-1*H*-indol-3-yl)propan-1-ol

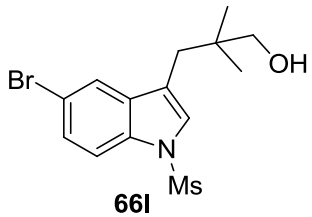
The title compound was prepared in the same procedure as described above in the preparation of compound **6e** to generate **7e** in 9% yield followed by **Method A** in 100% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.39-7.32 (m, 2H), 7.26 (s, 1H), 3.39 (s, 2H), 3.07 (s, 3H), 2.72 (s, 2H), 0.96 (s, 6H).



7j

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

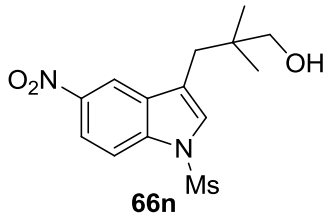
The title compound was prepared in the same procedure as described above in the preparation of compound **6j** in 7% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.84 (dd, J_1 = 9.0 Hz, J_2 = 4.2 Hz, 1H), 7.25 (s, 1H), 7.20 (dd, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H), 7.09 (td, J_1 = 9.0 Hz, J_2 = 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 $C_{14}H_{17}FNO_3S^+$ 298.0913, found 298.0919.



66l

3-(5-Bromo-1-(methylsulfonyl)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-ol

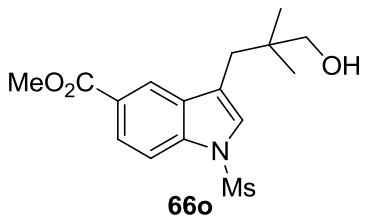
The title compound was prepared in the same procedure as described above in the preparation of compound **6l** to generate **7l** in 11% yield followed by **Method A** in 100% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 1.8 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.44 (dd, J_1 = 8.7 Hz, J_2 = 1.8 Hz, 1H), 7.24 (s, 1H), 3.35 (s, 2H), 3.06 (s, 3H), 2.66 (s, 2H), 0.94 (s, 6H).



66n

2,2-Dimethyl-3-(1-(methylsulfonyl)-5-nitro-1*H*-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, $CDCl_3$): δ 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 $C_{14}H_{19}N_2O_5S^+$ 327.1015, found 327.1012.



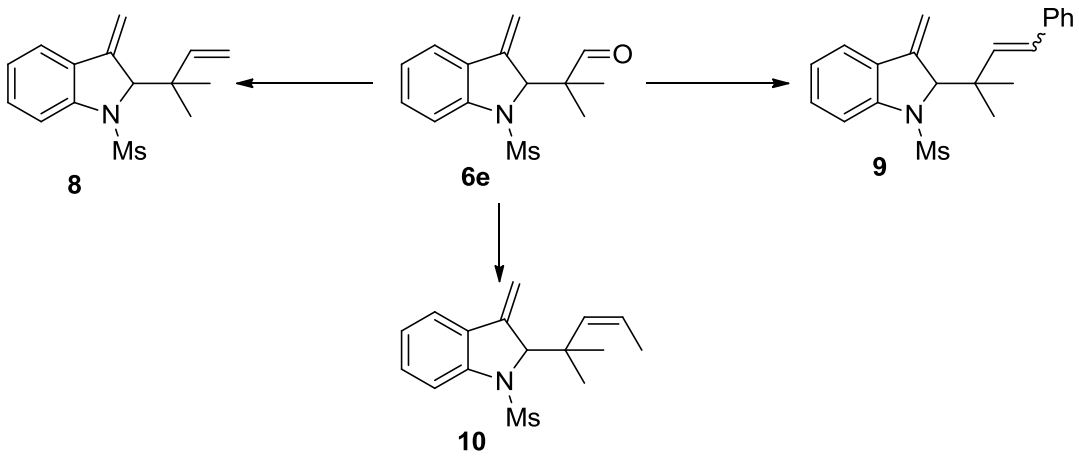
66o

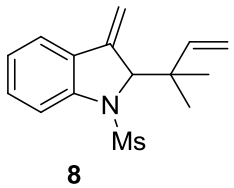
Methyl 3-(3-hydroxy-2,2-dimethylpropyl)-1-(methylsulfonyl)-1*H*-indole-5-carboxylate

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, $CDCl_3$): δ 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 $C_{16}H_{22}NO_5S^+$ 340.1219, found 340.1220.

1.6.6 Derivatization of compound 6e

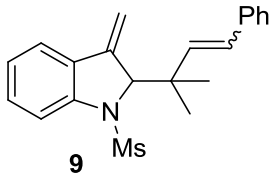
1.6.6.1 Procedure for preparation of 2-*tert*-prenylated indolines through Wittig reactions





2-(2-Methylbut-3-en-2-yl)-3-methylene-1-(methylsulfonyl)indoline

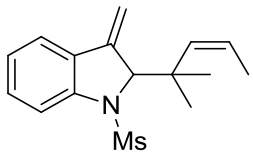
To a stirred suspension of methyltriphenylphosphonium bromide (93 mg, 0.26 mmol) in anhydrous THF (2 mL) at 0 ℃ was added 1.6M n-BuLi in hexanes (165 μL, 0.26 mmol) dropwise. The reaction mixture was stirred at the same temperature for 30 min with the formation of a bright yellow coloration. A solution of compound **6e** (56 mg, 0.2 mmol) in anhydrous THF (1 mL) was added dropwise. After stirring for 1 hour at 0 ℃, the reaction mixture was allowed to warm to rt and stirred at rt for 2 hours. Then, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (10 mL) and extracted with EtOAc for three times. The combined organic phase was washed with brine, dried over anhydrous $NaSO_4$ 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). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.28 (td, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.16 (td, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 1H), 5.75 (dd, J_1 = 17.1 Hz, J_2 = 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, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 4.42 (t, J = 1.5 Hz, 1H), 2.56 (s, 3H), 1.14 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 107.8 (CH_2), 74.5 (CH), 42.3 (C), 35.0 (CH_3), 24.3 (CH_3), 21.9 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{15}H_{20}NO_2S^+$ 278.1215, found 278.1211.



9

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, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{21}H_{24}NO_2S^+$ 354.1528, found 354.1531.



10

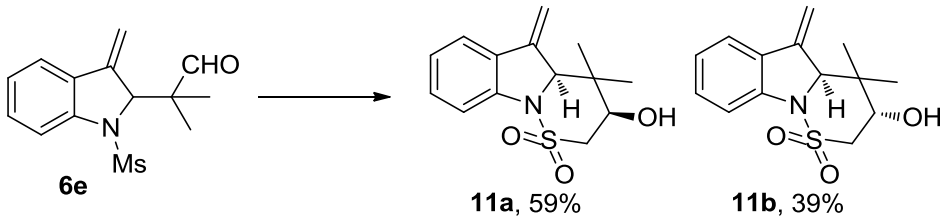
(Z)-3-Methylene-2-(2-methylpent-3-en-2-yl)-1-(methylsulfonyl)indoline

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 $C_{16}H_{22}NO_2S^+$ 292.1371, found 292.1374.

Table 1.6.6.1.1: NOE of compound **10** ($CDCl_3$)

Irradiated (ppm)	Observed (ppm)
5.19 (dd, 1H)	5.47-5.38 (m, 1H), 4.62 (s, 1H), 1.31 (s, 3H), 0.95 (s, 3H)
1.76 (dd, 3H)	5.47-5.38 (m, 1H), 4.62 (s, 1H), 1.31 (s, 3H), 0.95 (s, 3H)

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_4Cl aqueous solution and extracted with EtOAc for three times. The combined organic phase was washed with water and brine,

dried over anhydrous Na_2SO_4, 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**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.20 (td, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.97 (td, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 1H), 5.66 (d, *J* = 2.1 Hz, 1H), 5.14 (d, *J* = 1.8Hz, 1H), 4.46 (t, *J* = 2.0 Hz, 1H), 4.20-4.13 (m, 1H), 3.46 (dd, J_1 = 12.9 Hz, J_2 = 4.2 Hz, 1H), 3.20 (dd, J_1 = 12.9 Hz, J_2 = 11.6 Hz, 1H), 2.03 (m, 1H), 1.25 (s, 3H), 0.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3 (C), 141.3 (C), 130.3 (CH), 127.9 (C), 122.6 (CH), 120.5 (CH), 112.0 (CH), 106.4 (CH_2), 73.4 (CH), 70.1 (CH), 53.1 (CH_2), 40.9 (C), 20.1 (CH_3), 11.4 (CH_3). MS (ESI^+) m/z $(M+Na)^+$ calcd for $C_{14}H_{17}NNaO_3S^+$ 302.0827, found 302.0829. The relative configuration was determined by 1D-NOE spectra (Table 1.6.6.2.1).

Table 1.6.6.2.1: NOE of compound **11a** ($CDCl_3$)

Irradiated (ppm)	Observed (ppm)
0.67 (s, 3H)	3.20 (dd, 1H),1.25 (s, 3H)
1.25 (s, 3H)	5.14 (d, 1H), 4.46 (t, 1H), 0.67 (s, 3H)

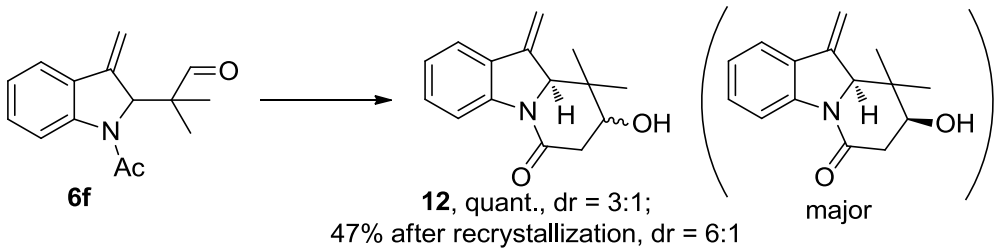
Compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.21 (td, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 6.98 (td, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 1H), 5.63 (d, *J* = 2.4 Hz, 1H), 5.10 (d, *J* = 1.8Hz, 1H), 4.96 (t, *J* = 1.8 Hz, 1H), 3.93 (dt, J_1 = 10.2 Hz, J_2 = 3.3 Hz, 1H), 3.78 (d, *J* = 10.2 Hz, 1H), 3.57 (dd, J_1 = 13.8 Hz, J_2 = 3.3 Hz, 1H), 3.38 (dd, J_1 = 14.1 Hz, J_2 = 3.6 Hz, 1H), 1.25 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.2 (C), 141.8 (C), 130.3 (CH), 127.9 (C), 122.7 (CH), 120.6 (CH), 112.0 (CH), 105.4 (CH_2), 76.3 (CH), 68.7 (CH), 51.4 (CH_2), 38.9 (C), 21.2 (CH_3),

18.8 (CH_3). MS (ESI^+) m/z $(M+Na)^+$ calcd for $C_{14}H_{17}NNaO_3S^+$ 302.0827, found 302.0816. The relative configuration was determined by 1D-NOE spectra (Table 1.6.6.2.2).

Table 1.6.6.2.2: NOE of compound **11b** ($CDCl_3$)

Irradiated (ppm)	Observed (ppm)
0.75 (s, 3H)	3.93 (dt, 1H), 3.57 (dd, 1H), 1.25 (s, 3H)
1.25 (s, 3H)	5.10 (d, 1H), 4.96 (t, 1H), 0.75 (s, 3H)

1.6.6.3 Procedure for preparation of indoline-fused lactams



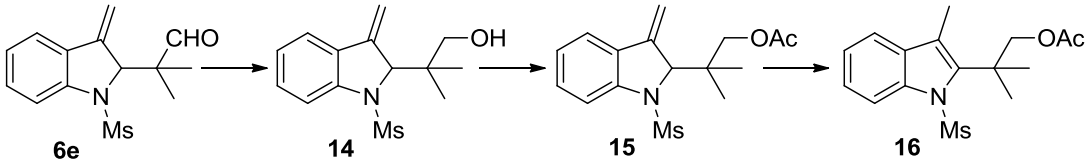
A solution of compound **6f** (13 mg, 0.053 mmol) and K_2CO_3 (11 mg, 0.08 mmol) in MeOH (0.5 mL) was stirred at 50 ℃ for 1 h. Solvent was removed and the residue was submitted to chromatography to give compound **12** (12.5 mg, 100% yield) as a mixture of distereomers (*dr* = 3:1). The product was purified by recrestallization to afford compound **12** (5.9 mg, 47% yield) as a mixture of distereomers (*dr* = 6:1). ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_1 = 18.3 Hz, J_2 = 7.5 Hz, 1H), 2.51 (dd, J_1 = 18.3 Hz, J_2 = 8.7 Hz, 1H), 1.38 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 72.9 (CH), 68.7 (CH), 39.8 (C), 39.4 (CH_2), 22.2 (CH_3), 11.8 (CH_3). MS (ESI^+)

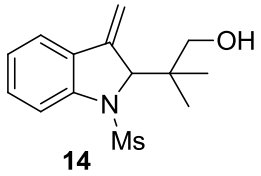
m/z $(M+H)^+$ calcd for $C_{15}H_{18}NO_2^+$ 244.1338, found 244.1338. The relative configuration of the major diastereomer was determined by 1D-NOE spectra (Table 1.6.6.3.1).

Table 1.6.6.3.1: NOE of compound **12** ($CDCl_3$)

Irradiated (ppm)	Observed (ppm)
0.77 (s, 3H)	2.51 (dd, 1H), 1.38 (s, 3H)
1.38 (s, 3H)	5.23 (d, 1H), 4.42 (t, 1H), 3.88 (t, 1H), 0.77 (s, 3H)

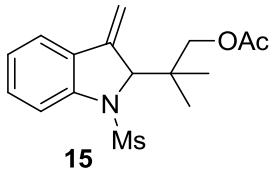
1.6.6.4 Procedure for preparation of re-aromatized indole 16





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

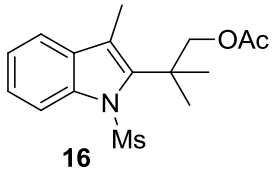
The title compound was prepared in the same procedure as described above in **Method A** in 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 5.70 (d, J = 1.5 Hz, 1H), 5.19 (s, 1H), 4.62 (s, 1H), 3.94 (dd, 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).



15

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_2Cl_2 (1 mL) was added DMAP (67.5 mg, 0.55 mmol) followed by Ac_2O (47.5 μL, 0.5 mmol) at 0 ^oC. This reaction mixture was stirred for 0.5 h at 0 ^oC, and then poured into a saturated aqueous solution of NH_4Cl, extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered. The solvent was removed under reduced pressure. The residue was submitted to chromatography to give compound **15** (80.2 mg, 100% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 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).



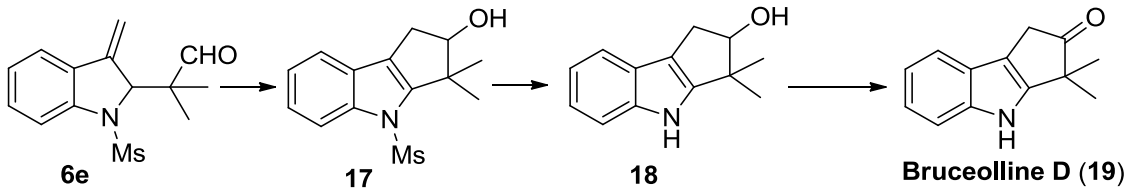
16

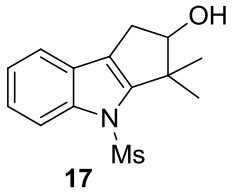
2-Methyl-2-(3-methyl-1-(methylsulfonyl)-1*H*-indol-2-yl)propyl acetate

To a solution of compound **15** (12.6 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (1 mL) was added 0.1M $TiCl_4$ in anhydrous CH_2Cl_2 (78 μL, 0.008 mmol) at rt. The reaction was

stirred at rt for 18 h before iced $NaHCO_3$ aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, 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, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 39.7 (C), 35.3 (CH_3), 28.4 (CH_3), 21.1 (CH_3), 12.5 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{16}H_{22}NO_4S^+$ 324.1270, found 324.1267.

1.6.6.5 Procedure for preparation of Bruceolline D

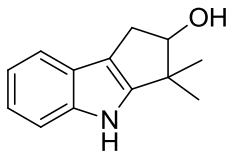




3,3-Dimethyl-4-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-2-ol

To a solution of compound **6e** (14 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (1 mL) was added 0.1M $TiCl_4$ in anhydrous CH_2Cl_2 (0.1 mL, 0.01 mmol) at rt. The reaction was stirred at rt for 2 h before iced $NaHCO_3$ aqueous solution was added to quench the

reaction. The mixture was extracted with EtOAc, washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product **17** (13.6 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_1 = 15.0 Hz, J_2 = 6.6 Hz, 1H), 3.04 (s, 3H), 2.60 (dd, J_1 = 15.0 Hz, J_2 = 6.6 Hz, 1H), 1.52 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_3), 31.4 (CH_2), 25.5 (CH_3), 19.2 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{14}H_{18}NO_3S^+$ 280.1007, found 280.1006.

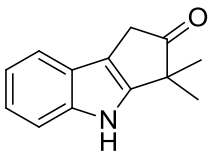


18

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 CH_2Cl_2. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was submitted to chromatography to give compound **18** (15.9 mg, 74% yield). ^{1}H NMR (300 MHz, $CDCl_3$): 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, J_1 = 14.4 Hz, J_2 = 6.9 Hz, 1H), 2.67 (dd, J_1 = 14.4 Hz, J_2 = 6.0 Hz, 1H), 1.37 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 25.5 (CH_3), 20.5 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{13}H_{16}NO^+$ 202.1232, found 202.1231.



Bruceolline D (19)

3,3-Dimethyl-3,4-dihydrocyclopenta[*b*]indol-2(1*H*)-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 Na_2SO_4, 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, $CDCl_3$): δ 8.07 (br, 1H), 7.52 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 7.41 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 7.24-7.14 (m, 2H), 3.55 (s, 2H), 1.39 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 24.1 (CH_3). Spectral data were in accordance with those in literature.[17] MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{13}H_{14}NO^+$ 200.1075, found 200.1073.

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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.[4b] 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.

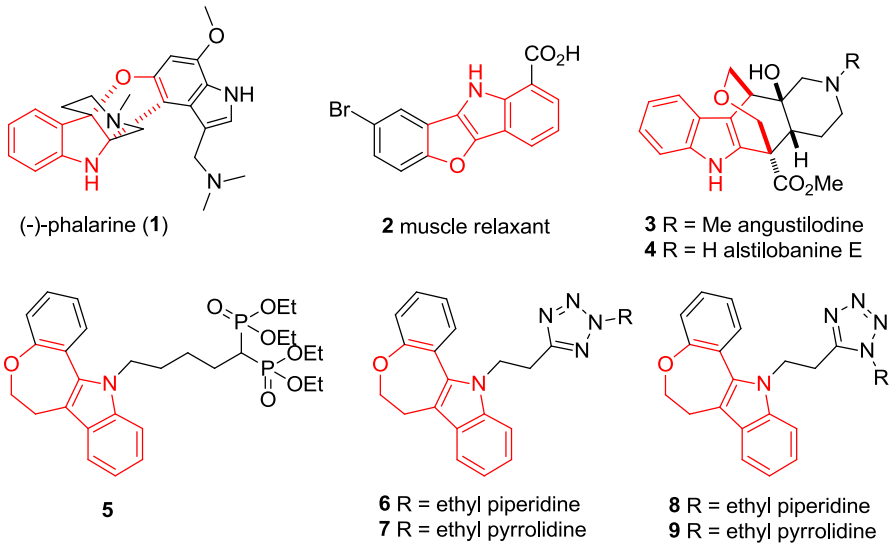
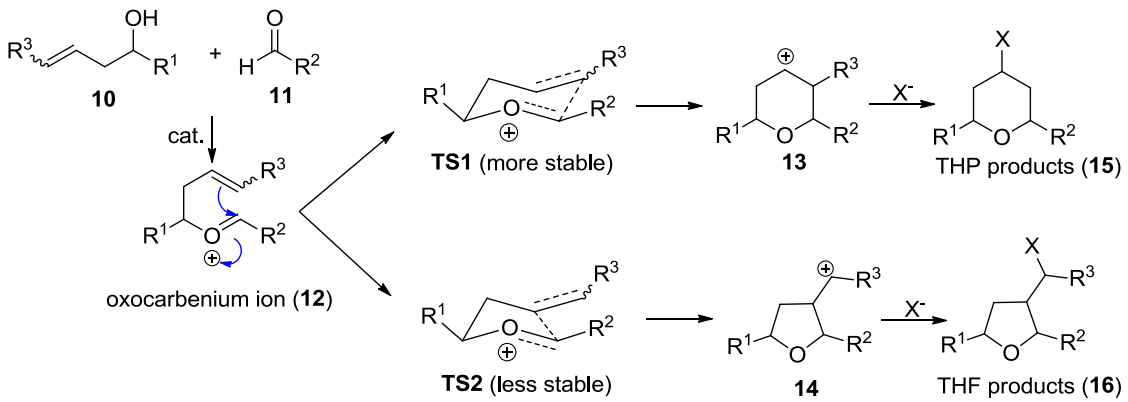


Figure 2.1.1 Some natural products and biologically active compounds

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.[7] 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-memebred 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 R^3 in **TS1**. As a result, a mixture of tetrahydropyran and tetrahydrofuran is generated.[8] THF products can be formed exclusively when substituents on the

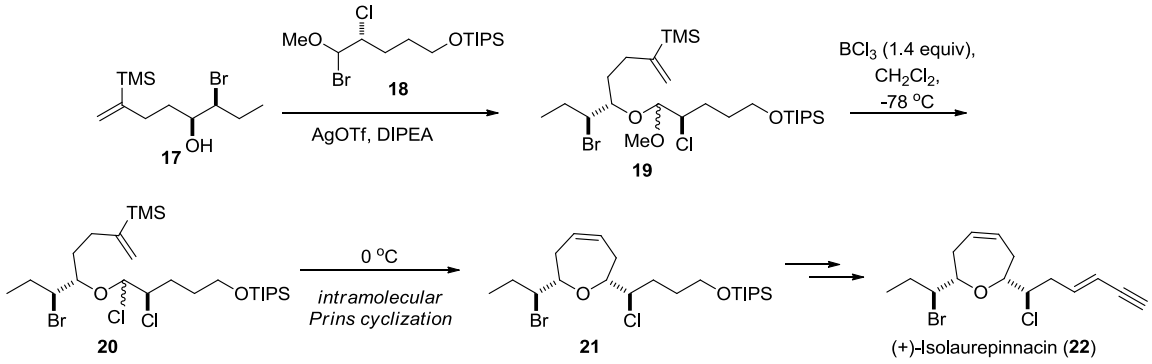
homoallylic acohol meet some particular requirements to stabilize the exocyclic carbocation **14** (i.e., R^3 = OH, OR,[9] CH_2SiR_3,[10] Ar[11] and terminally dialkyl groups[12]). Therefore, the regioselectivity of the ring-size between THP and THF is dependent on the structure of homoallylic alcohol. To the best of our knowledge, no studies have been reported to synthesize respective THPs and THFs from the same homoallylic alcohol precursors.



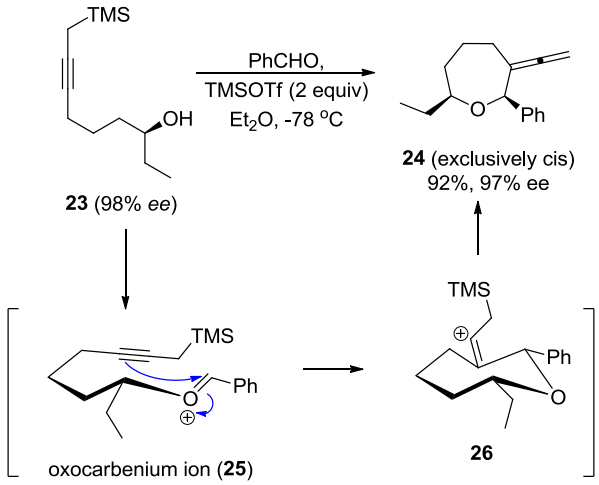
Scheme 2.1.1 General mechanism and regioselectivity of Prins cyclization

Compared with six-membered THP rings, seven-membered cyclic ethers are less stable as a result of transannular (Prelog),[13] bond (Baeyer), and torsional (Pitzer) strains.[14] 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.[15] 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.[15b-d] A Prins cyclization precursor **20** was prepared from a

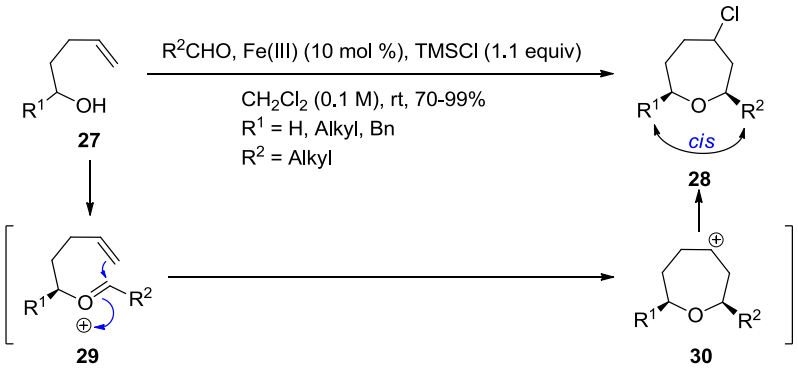
silyl activated 4-alken-1-ol **17** which allows intramolecular cyclization to happen under the promotion of an excess of BCl_3 (Scheme 2.1.2). Obviously, the precursors are not easily accessible in such methodologies. Direct and simple methodologies to give seven-membered cyclic ethers via intermolecular 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 cyclization[15d]



Scheme 2.1.3 Synthesis of oxepane **24** from propargylsilane **23**[16a]



Scheme 2.1.4 Iron (III)/trimethylsilyl chloride-catalyzed direct synthesis of oxepanes[16b]

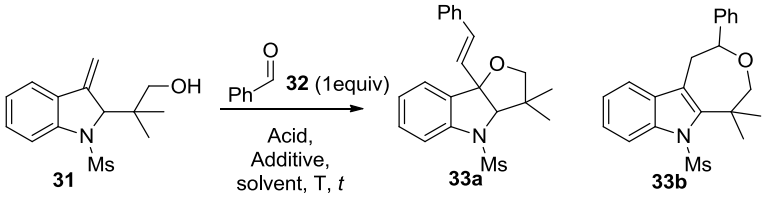
To the best of our knowledge, examples of regioselectivity of ring-size using Prins cyclization from same unsaturated alcohols have not been reported. Herein, we report a divergent Prins cyclization via a classic and an usual procedure to give seven-membered cyclic ethers and five-membered tetrahydrofurans, 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.[a]



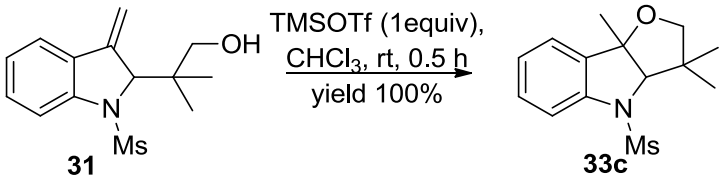
Entry	Acid	Solvent	T (^{o}C)	*t* (h)	33a : 33b[b]	(33a + 33b) Yield (%)[c]
1	2M H_2SO_4 aq.	DCM	rt	1	decomposed	-
2	1 equiv. HF·Py	$CHCl_3$	rt	3	decomposed	-
3	100 equiv. AcOH	DCM	rt	48	No rxn	-
4	100 equiv. TFA	DCM	rt	0.5	0.8 : 1	59
5	3 equiv. PhCOOH	PhH	80	16	No rxn	-
6	3 equiv. pTsOH	$PhCH_3$	60	3	decomposed	-
7	3 equiv. 10-CSA	PhH	80	20	2 : 1	55
8	3 equiv. MsOH	DCM	rt	1	1.4 : 1	73
9	0.3 equiv. $BF_3 \cdot Et_2O$	DCM	rt	1	3 : 1	66
10	0.3 equiv. TMSOTf	DCM	rt	2	4 : 1	25[d]
11	0.3 equiv. $FeCl_3$	DCM	rt	0.5	1 : 1.4	56

12	0.2 equiv. $TiCl_4$	DCM	rt	6	1 : 4	17
13	3 equiv. $ZnCl_2$	$CHCl_3$	rt	24	1.4 : 1	29

[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.

When treated with inorganic acid like H_2SO_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 trifluoro acetic 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 wat 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).

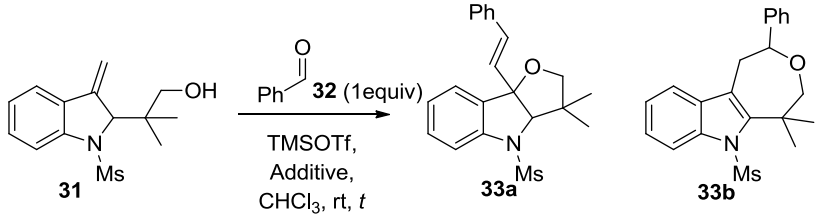


Scheme 2.2.1 Generation of product **33c**.

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]



Entry	TMSOTf Equiv.	Additive	*t* (h)	33a : 33b[b]	(33a + 33b) Yield (%)[c]
1	1	-	2	5 : 1	75
2	2	-	16	Only **33a**	71[e]
3	3	-	16	Only **33a**	33[e]
4	2	0.2 equiv PhCOOH	16	Only **33a**	71[e]
5	2	0.2 equiv Py	16	Only **33a**	73[e]
6	2	1 equiv Py	16	5 : 1	79
7	3	1 equiv Py	16	Only **33a**	83[e]
8	3	1 equiv Py	10 min	2.2 : 1	85
9	3	1 equiv Py + 2 μL H_2O	16	5 : 1	50
10	3	1 equiv Py + 4Å MS	16	Only **33a**	91[e]

[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.

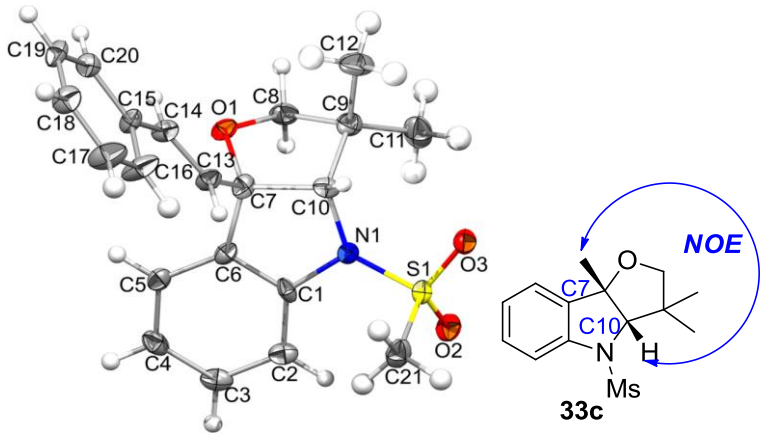
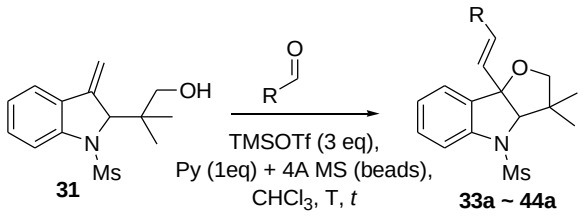


Figure 2.2.1 Crystal structure of **33a** and NOE for **33c**.

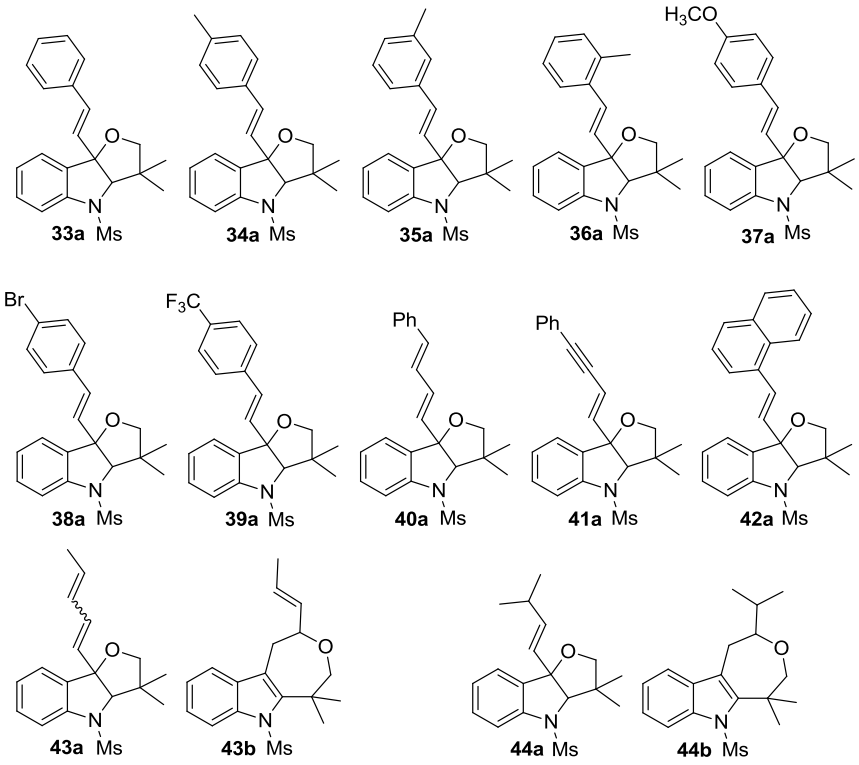
The scope of the reactions was probed accordingly (Table 2.2.3). Various substitution pattern on the benzene ring in benzaldehydes can be tolerated (Table 2.2.3, entry 2 to 4). The reaction worked well with strong electron-donating and weak electron-withdrawing groups (Table 2.2.3, entry 5 and 6). Strong 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]



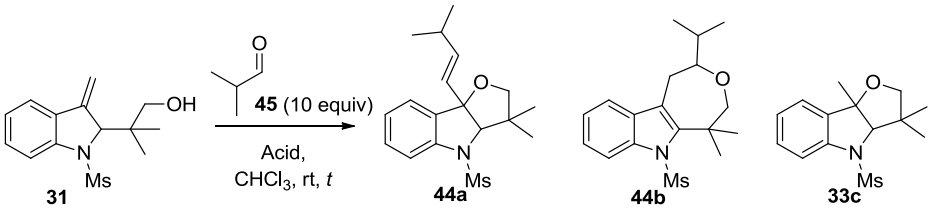
Entry	R	T (^{o}C)	*t* (h)	a : b[b]	Yield (%)[c]
1	Ph-	rt	16	Only **33a**	91
2	*p*-CH_3Ph-	rt	16	Only **34a**	91
3	*m*-CH_3Ph-	rt	16	Only **35a**	91
4	*o*-CH_3Ph-	rt	16	Only **36a**	91
5	*p*-CH_3OPh-	rt	2	Only **37a**	95
6	*p*-BrPh-	rt	16	Only **38a**	93
7	*p*-CF_3Ph-	rt	16	Only **39a**	63
8	PhCH=CH-	0	5 min	Only **40a**	91
9	PhC≡C-	rt	16	Only **41a**	92
10	naphthalen-1-yl	rt	16	Only **42a**	94
11	CH_3CH=CH-	0	10 min	**43a** : **43b** = 7 : 1	63[d]
12	$(CH_3)_2$CH-	rt	5 min	**44a** : **44b** = 1 : 2.5	13

[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, $ZnCl_2$ 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]



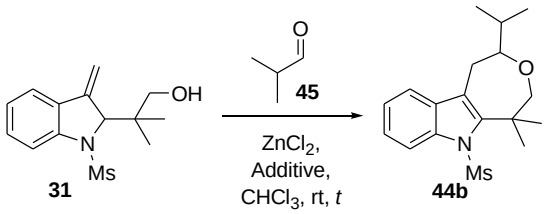
Entry	Acid	*t*	44a : 44b : 33c[b]
1	TsOH·Py	24 h	No reaction
2	3eq. MsOH	5 min	1 : 1.3 : 0
3	100eq. TFA	24 h	**33c** is dominant

4	3eq. Binol-Phosphoric acid	48 h	No reaction
5	3eq. BF_3 ŁEt_2O	1 h	1 : 1.7 : 0
6	3eq. $ZnCl_2$	24 h	1 : 13 : 0
7	3eq. $FeCl_3$	7 h	**33c** is dominant
8	3eq. $AlCl_3$	6 h	Very messy
9	3eq. $CuCl_2$	43 h	**33c** is dominant
10	3eq. $CuBr_2$	43 h	messy
11	3eq. $HgCl_2$	43 h	No reaction
12	3eq. $BiCl_3$	6 h	1 : 2 : 0
13	3eq. $SnCl_2$	43 h	1 : 6 : 0.5
14	3eq. $InCl_3$	12 h	1 : 5 : 0.5

[a] The reactions were carried out on a 0.025-mmol scale of **31** and monitored by appearance of **44a** and **44b** by TLC and ^{1}HNMR spectroscopy. [b]The ratio of **44a** : **44b** : **33c** was determined by crude ^{1}HNMR spectroscopy.

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 ^{o}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 2.2.5: Optimization of reaction conditions for selective synthesis of **44b**.[a]

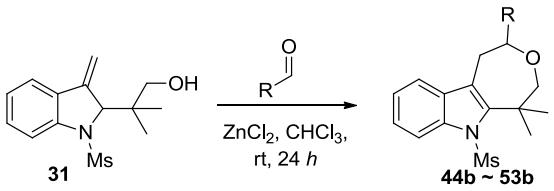


Entry	Equiv of 45	Equiv of $ZnCl_2$	Solvent	T (^oC)	Additive	*t (h)*	Yield (%)[b]
1	10	3	CH_3CN	rt	-	15	No reaction
2	10	3	DMSO	rt	-	15	No reaction
3	10	3	DMF	rt	-	15	No reaction
4	10	3	$PhCH_3$	rt	-	16	72
5	10	3	$CHCl_3$	rt	-	24	73
6	10	3	$CHCl_3$	rt	4Å MS powder	27	< 10[c]
7	10	3	$CHCl_3$	rt	1 equiv py	24	No reaction
8	10	3	$CHCl_3$	4	-	72	< 70[c]
9	10	3	$CHCl_3$	50	-	8	69
10	5	3	$CHCl_3$	rt	-	24	73
11	5	1.5	$CHCl_3$	rt	-	24	73
12	5	0.3	$CHCl_3$	rt	-	24	No reaction
13	2	1.5	$CHCl_3$	rt	-	24	56

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

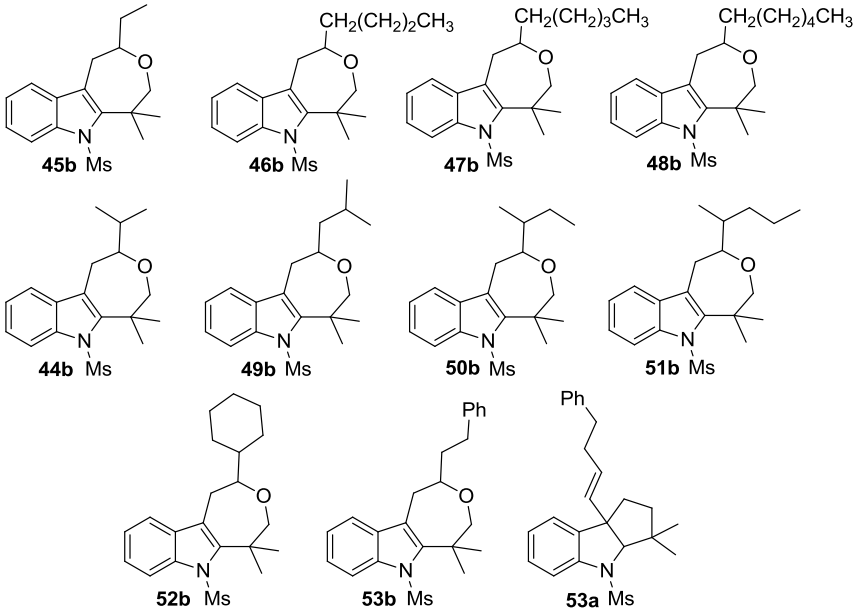
The optimized protocol can be employed for the reactions of a variety of alkyl aldehydes and indoline **31** (Table 2.2.6). The reaction worked well with both linear and branched aliphatic aldehydes (Table 2.2.6, entries 1 to 9). But hydrocinnamaldehyde delivered a lower yield due to the increasing generation 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]

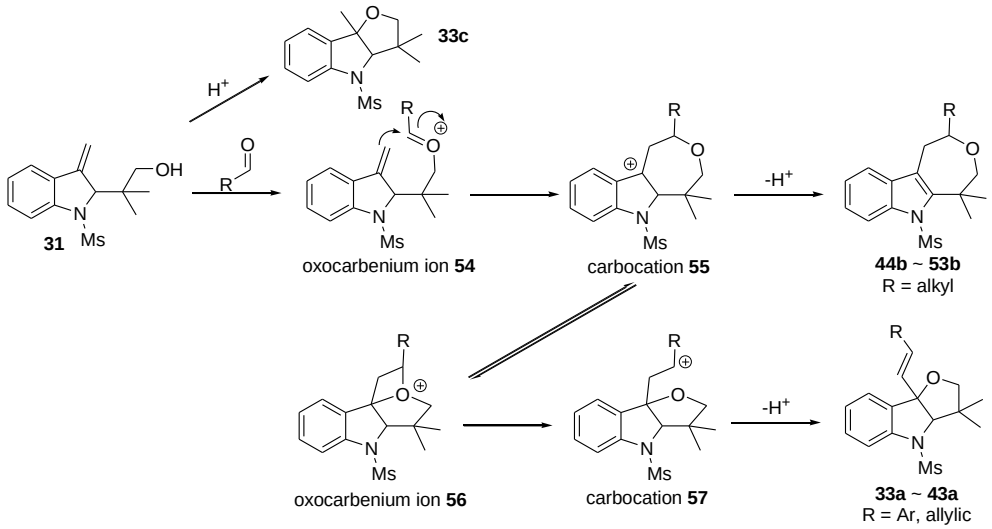


Entry	R		Yield (%)[b]
1	$(CH_3)_2CH$-	**44b**	73
2	CH_3CH_2-	**45b**	76
3	$CH_3(CH_2)_2CH_2$-	**46b**	72
4	$CH_3(CH_2)_3CH_2$-	**47b**	75
5	$CH_3(CH_2)_4CH_2$-	**48b**	69
6	$(CH_3)_2CHCH_2$-	**49b**	75
7	$CH_3CH_2(CH_3)CH$-	**50b**	68[c]
8	$CH_3(CH_2)_2(CH_3)CH$-	**51b**	77[c]
9	*c*-C_6H_{11}-	**52b**	69
10	$PhCH_2CH_2$-	**53b**	49
11	Ph-	**33b**	12

[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.



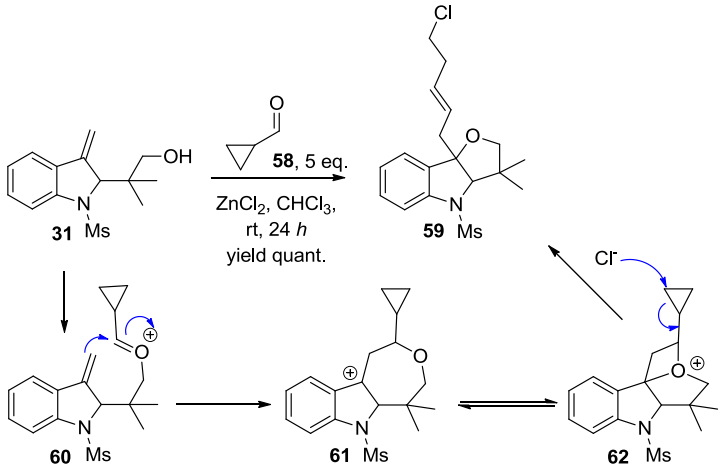
Because observed **33b** could be transformed into **33a** (Table 2.2.2, entry 1, 2, 7 and 8), we proposed that the reaction of indoline **31** and an aldehyde generates the oxocarbenium ion **54** which evolves to the corresponding seven-membered cyclic ethers **44b** to **53b** via the carbocation **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.



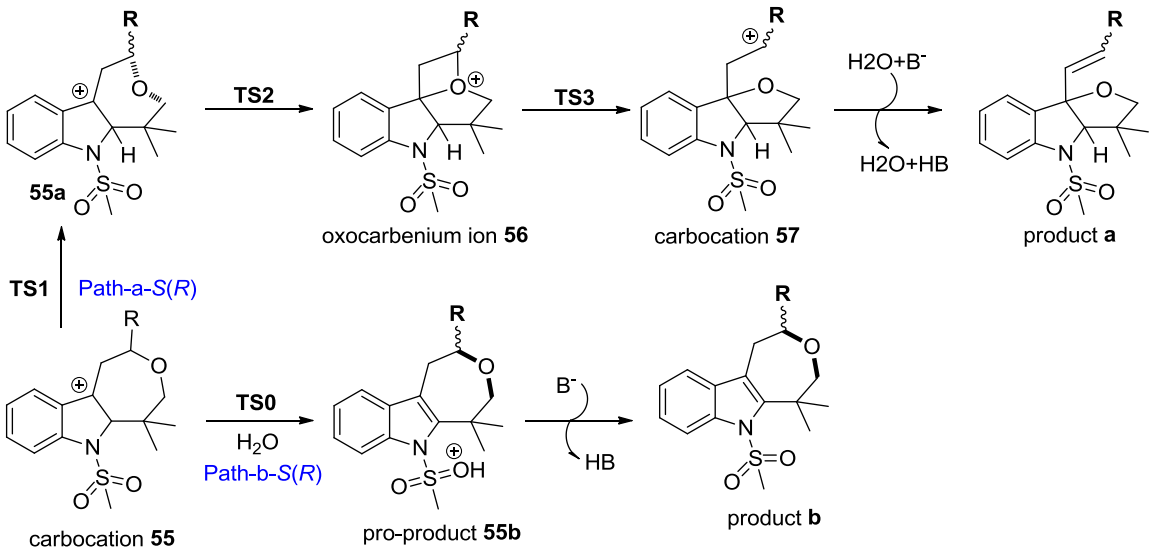
Scheme 2.2.3 Proposed mechanism for synthesis of **59**

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**

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.

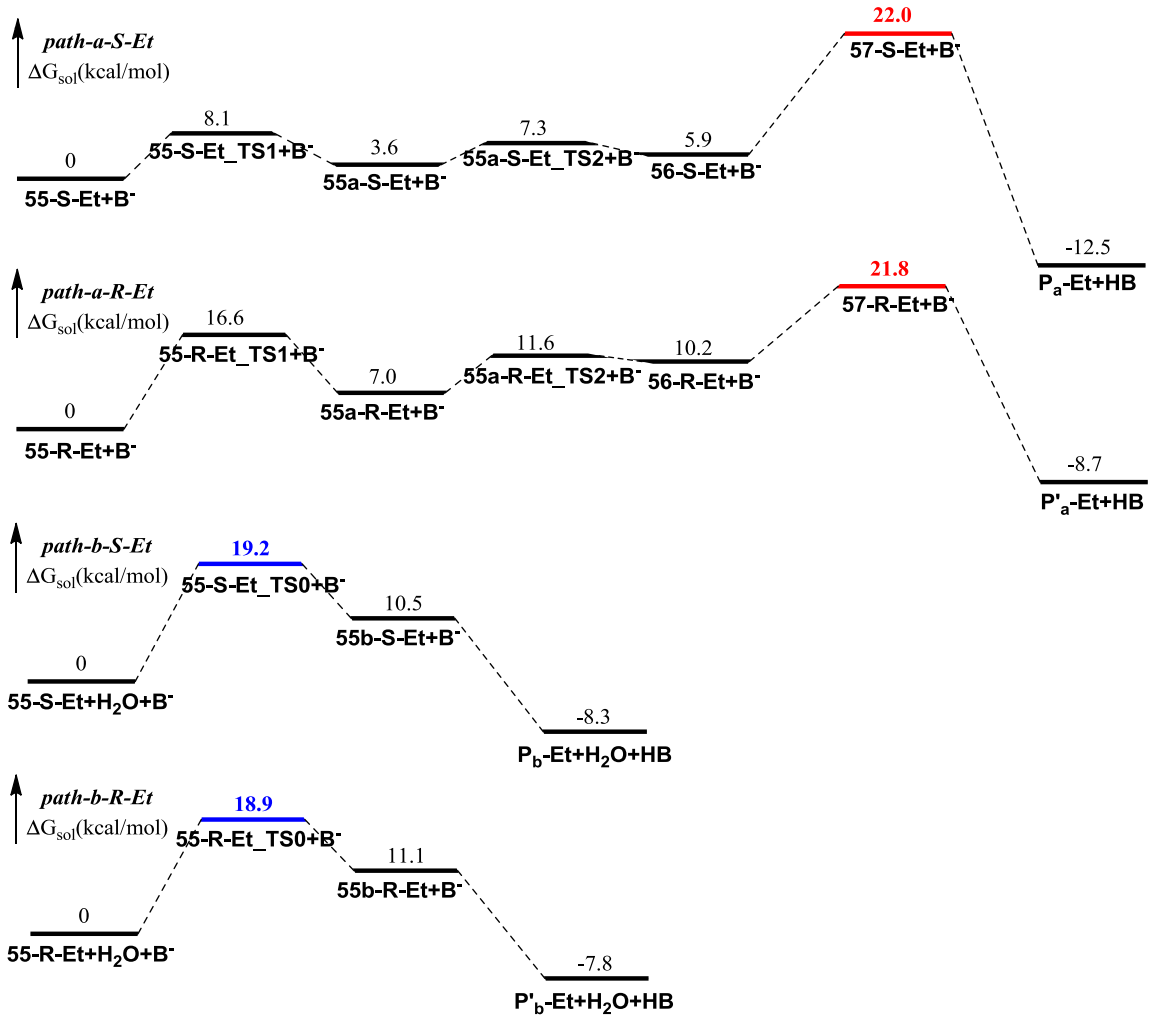


Figure 2.3.1 Free energy profiles of carbocation **55** with ethyl group

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^a 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.

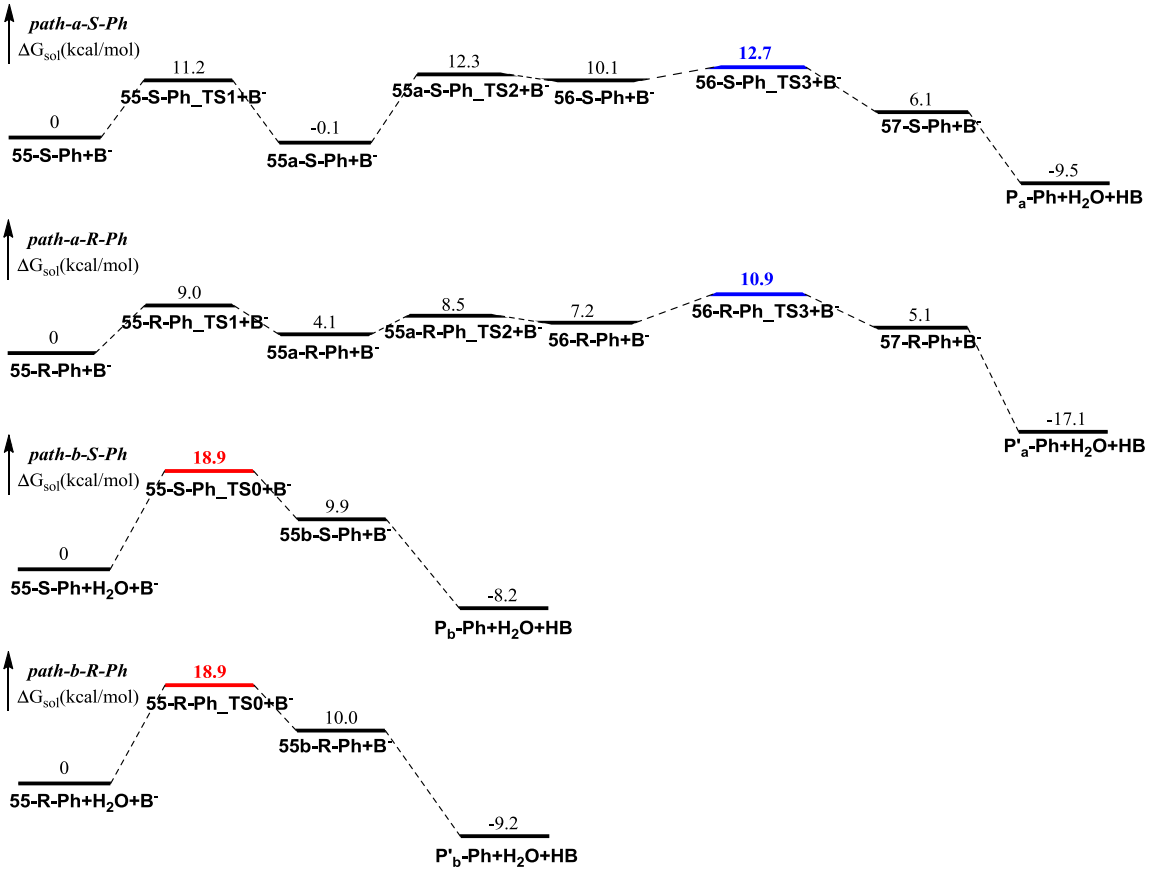
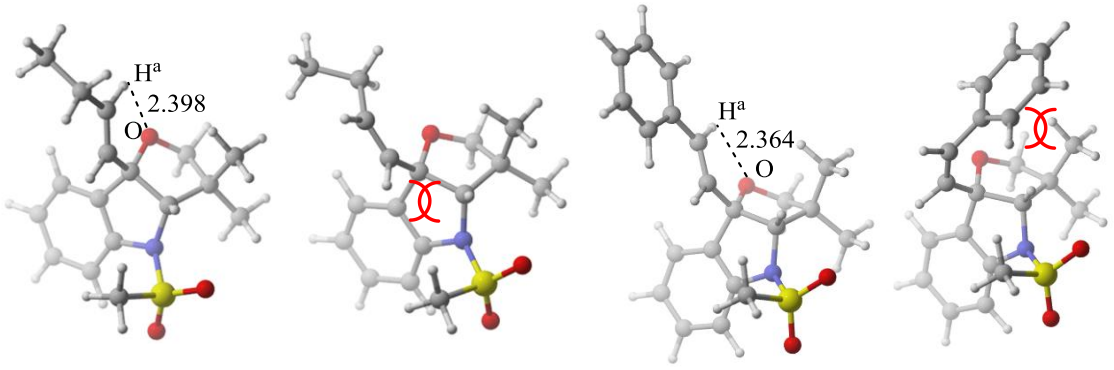


Figure 2.3.2 Free energy profiles of carbocation **55** with phenyl group



trans-Et (P_a-Et) ΔG=0 kcal/mol ΔG_{sol}=0 kcal/mol

cis-Et (P'_a-Et) ΔG=3.2 kcal/mol ΔG_{sol}=2.8 kcal/mol

trans-Ph (P'_a-Ph) ΔG=0 kcal/mol ΔG_{sol}=0 kcal/mol

cis-Ph (P_a-Ph) ΔG=7.9 kcal/mol ΔG_{sol}=6.4 kcal/mol

Figure 2.3.3 Optimized structures of *cis* and *trans* products **a**: free energy in gas and solution (PCM model) are shown.

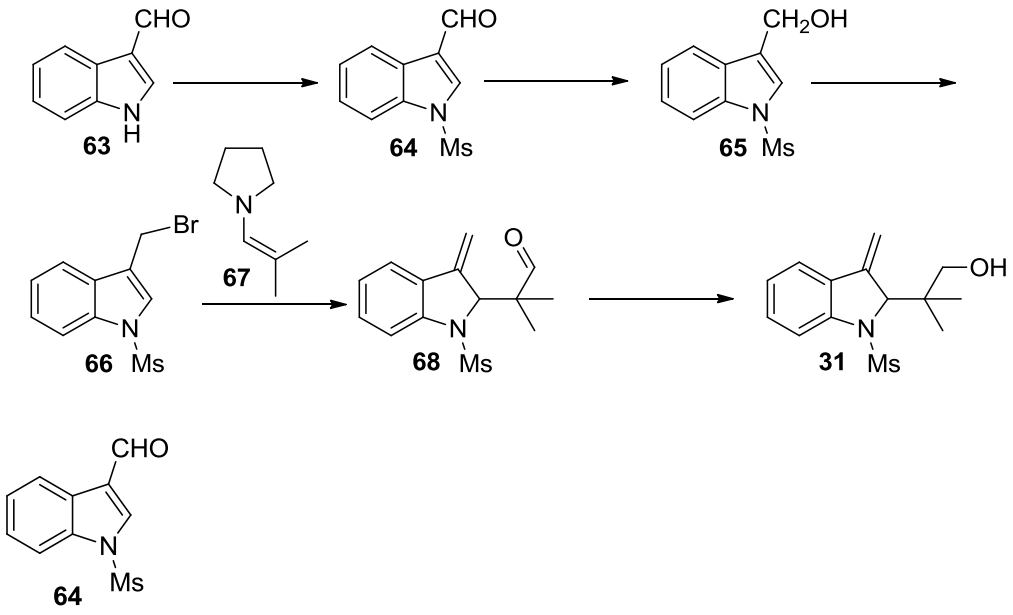
2.4 Conclusions

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

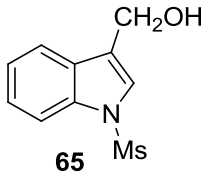
General Information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F_{254} were used for thin-layer chromatography (TLC) analysis. Visualisation was effected with ultraviolet light, 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. $CDCl_3$ (δ = 7.26 and 77.0 for ^{1}H and ^{13}CNMR spectra respectively) and DMSO-d_6 (δ = 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.

2.5.1 Preparation of indoline substrate 31



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

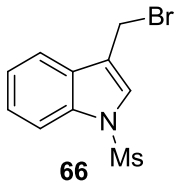
To a solution of aldehyde **63** (1.45 g, 10 mmol) and Et_3N (4.05 mg, 5.6 mL, 40 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 ℃ was added MsCl (2.34 μL, 30 mmol) dropwise. After addition, the reaction was warmed to room temperature and stirred for 30 min at rt. Ice-water was added to quench the reaction. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography to afford the desired product **64** (1.83 g, yield 82%). ^{1}H NMR (500 MHz, $CDCl_3$): 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).



65

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

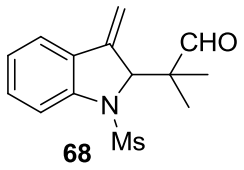
To a solution of aldehyde **64** (2.90 g, 20 mmol) in MeOH (20 mL) was added $NaBH_4$ (756 mg, 20 mmol) in some portions slowly within 30 min at 0 ℃. The reaction was continuted to stir at 0 ℃ for 30 min. Icy water 100 mL was added and a large amount of white precipitate formed. The mixture was filtered to afford pure alcohol **65** in 91% yield. ^{1}H NMR (300 MHz, $CDCl_3$): 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).



66

3-(Bromomethyl)-1-(methylsulfonyl)-1*H*-indole

To a solution of compound **65** (3.05 g, 13.5 mmol) in anhydrous CH_2Cl_2 (30 mL) was added PBr_3 (4.8 g, 1.7 mL, 17.6 mmol) at 0 ℃. 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_2SO_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, $CDCl_3$): δ 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).

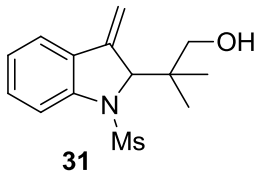


68

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_3CN (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_2O (0.6 mL), and the resulting solution was put into microwave condition (100 W, 100 ℃). 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_2SO_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, $CDCl_3$): 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 $C_{14}H_{18}NO_3S^+$ 280.1007, found 280.1008.



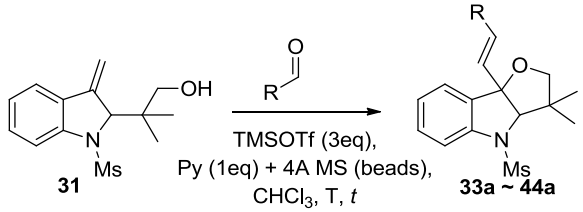
31

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

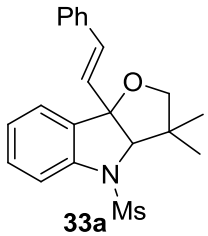
To a solution of aldehyde **68** (894 mg, 3.2 mmol) in MeOH was added $NaBH_4$ (121 mg, 3.2mmol) in some portions slowly within 30 min at 0 ℃. The reaction was continuted to stir at 0 ℃ for 30 min. Brine was added and extrated with EtOAc for three times. The organic layers were combined and dried over anhydrous Na_2SO_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, $CDCl_3$): 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). ^{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

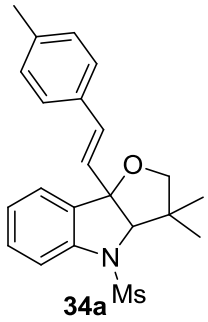


General Procedure: To a solution of compound **31** (21 mg, 0.075 mmol, 1 eq.) in anhydrous $CHCl_3$ (1.5 mL) was added aldehyde (0.075 mmol, 1 eq.), pyridine (6 μL, 0.075 mmol, 1 eq.), 4Å MS and TMSOTf (42 μL, 0.225 mmol, 3 eq.), sequentially. The reaction was stirred at room temperature or 0 ℃ for 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_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **33a** ~ **43a**.



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

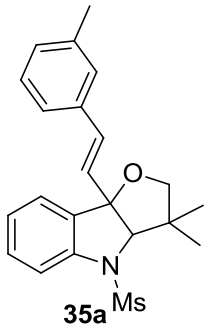
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 8.1 Hz, 1H), 7.41 – 7.19 (m, 8H), 6.47 (dd, J_1 = 27.6 Hz, J_2 = 15.9 Hz, 2H), 3.98 (s, 1H), 3.66 (d, J = 9 Hz, 1H), 3.19 (d, J = 9 Hz, 1H), 2.75 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6 (C), 135.9 (C), 132.6 (C), 130.9 (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 $C_{21}H_{24}NO_3S^+$ 370.1477, found 370.1480.



34a

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

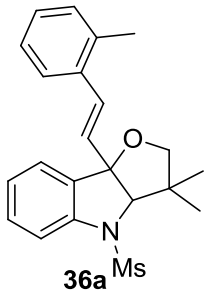
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.8 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.26 – 7.19 (m, 3H), 7.12 (d, J = 8.1 Hz, 2H), 6.42 (dd, J_1 = 30.0 Hz, J_2 = 15.9 Hz, 2H), 3.97 (s, 1H), 3.64 (d, J = 9 Hz, 1H), 3.18 (d, J = 9 Hz, 1H), 2.74 (s, 3H), 2.33 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (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 $C_{22}H_{26}NO_3S^+$ 384.1633, found 384.1634.



35a

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

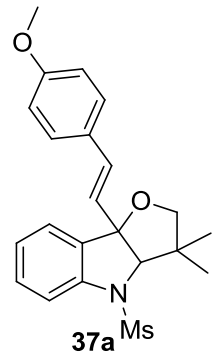
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 8.1 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.24 – 7.15 (m, 4H), 7.08 (d, J = 6.9 Hz, 1H), 6.45 (dd, J_1 = 38.7 Hz, J_2 = 15.9 Hz, 2H), 3.98 (s, 1H), 3.65 (d, J = 9 Hz, 1H), 3.19 (d, J = 9 Hz, 1H), 2.75 (s, 3H), 2.34 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (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 $C_{22}H_{26}NO_3S^+$ 384.1633, found 384.1631.



36a

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

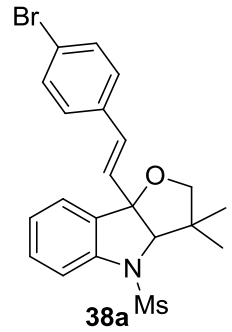
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.25 – 7.12 (m, 4H), 6.72 (d, *J* = 15.9 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 3.99 (s, 1H), 3.66 (d, *J* = 9 Hz, 1H), 3.20 (d, *J* = 9 Hz, 1H), 2.75 (s, 3H), 2.24 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{22}H_{26}NO_3S^+$ 384.1633, found 384.1635.



37a

(*E*)-8b-(4-Methoxystyryl)-3,3-dimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

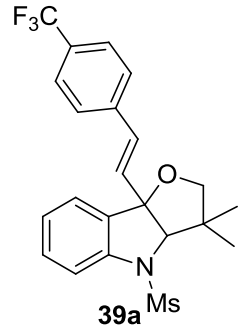
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.36 (dd, J_1 = 18 Hz, J_2 = 16.8 Hz, 2H), 3.97 (s, 1H), 3.80 (s, 3H), 3.64 (d, *J* = 9 Hz, 1H), 3.18 (d, *J* = 9 Hz, 1H), 2.74 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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).



38a

(*E*)-8b-(4-Bromostyryl)-3,3-dimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

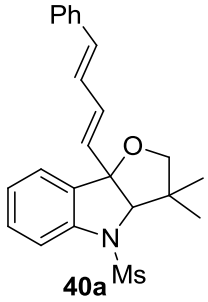
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.41 – 7.32 (m, 2H), 7.23 – 7.19 (m, 3H), 6.44 (dd, J_1 = 29.3 Hz, J_2 = 15.9 Hz, 2H), 3.98 (s, 1H), 3.64 (d, J = 9 Hz, 1H), 3.19 (d, J = 9 Hz, 1H), 2.75 (s, 3H), 1.25 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{21}H_{23}BrNO_3S^+$ 448.0582, found 448.0593.



39a

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

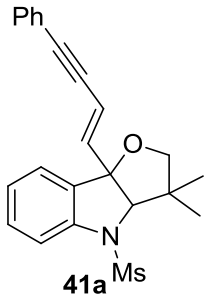
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 – 7.55 (m, 3H), 7.47 – 7.33 (m, 4H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.56 (dd, J_1 = 21.3 Hz, J_2 = 15.9 Hz, 2H), 4.00 (s, 1H), 3.66 (d, *J* = 9 Hz, 1H), 3.21 (d, *J* = 9 Hz, 1H), 2.77 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7 (C), 139.3 (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 $C_{22}H_{23}F_3NO_3S^+$ 438.1351, found 438.1352.



40a

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

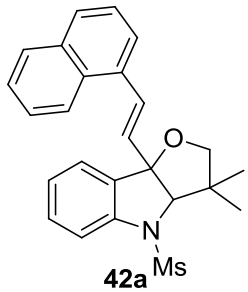
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.29 (m, 6H), 7.24 – 7.19 (m, 2H), 6.80 (dd, J_1 = 15.6 Hz, J_2 = 9.9 Hz, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.24 (dd, J_1 = 15.3 Hz, J_2 = 9.9 Hz, 1H), 6.12 (d, *J* = 15.3 Hz, 1H), 3.94 (s, 1H), 3.62 (d, *J* = 9 Hz, 1H), 3.16 (d, *J* = 9 Hz, 1H), 2.75 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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).



41a

(*E*)-3,3-Dimethyl-4-(methylsulfonyl)-8b-(4-phenylbut-1-en-3-yn-1-yl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

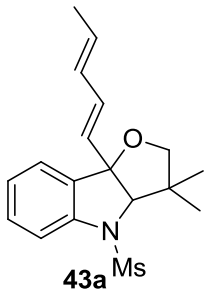
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 8.1 Hz, 1H), 7.42 – 7.31 (m, 7H), 7.20 (t, J = 7.5 Hz, 1H), 6.47 (dd, J_1 = 27.6 Hz, J_2 = 15.9 Hz, 2H), 6.47 (d, J = 15.6 Hz, 1H), 5.89 (d, J = 15.6 Hz, 1H), 3.97 (s, 1H), 3.62 (d, J = 9 Hz, 1H), 3.18 (d, J = 9 Hz, 1H), 2.78 (s, 3H), 1.236 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{23}H_{24}NO_3S^+$ 394.1477, found 394.1471.



42a

(*E*)-3,3-Dimethyl-4-(methylsulfonyl)-8b-(2-(naphthalen-1-yl)vinyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

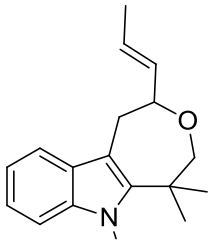
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 – 7.79 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.51 – 7.40 (m, 5H), 7.30 – 7.25 (m, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 4.06 (s, 1H), 3.71 (d, *J* = 9 Hz, 1H), 3.25 (d, *J* = 9 Hz, 1H), 2.79 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8 (C), 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 $C_{25}H_{26}NO_3S^+$ 420.1633, found 420.1633.



43a

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

^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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).

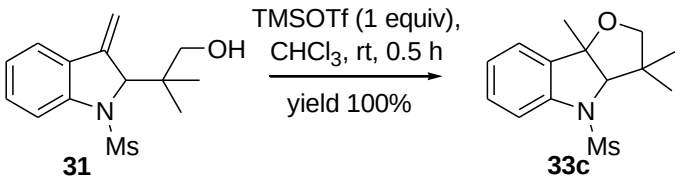


43b

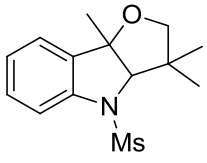
(*E*)-5,5-Dimethyl-6-(methylsulfonyl)-2-(prop-1-en-1-yl)-2,4,5,6-tetrahydro-1H-oxepino[4,5-b]indole

^{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



31 **33c**



33c

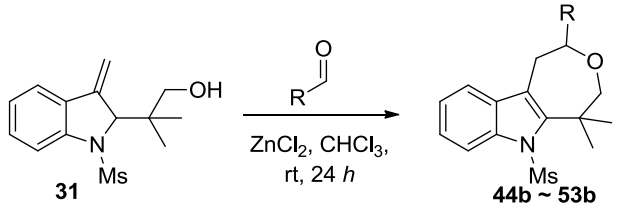
3,3,8b-Trimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

To a solution of compound **31** (21 mg, 0.075 mmol, 1 eq.) in anhydrous $CHCl_3$ (1.5 mL) was added 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 $NaHCO_3$ aqueous solution (5 mL) and extracted with DCM for 3 times. The organic layers were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **33c** (21 mg, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 8.1 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.17 (td, J_1 = 7.5 Hz, J_2 = 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 44.1 (C), 35.4 (CH_3), 26.9 (CH_3), 26.6 (CH_3), 20.4 (CH_3). MS (ESI^+) m/z $(M+H)^+$ calcd for $C_{14}H_{20}NO_3S^+$ 282.1164, found 282.1165.

Table 2.5.3.1 NOE of compound **33c** ($CDCl_3$)

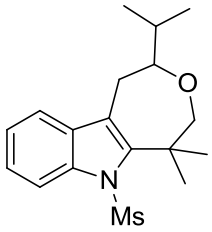
Irradiated (ppm)	Observed (ppm)
3.78 (s, 1H)	2.77 (s, 3H), 1.72 (s, 3H), 1.23 (s, 3H)
1.72 (s, 3H)	3.78 (s, 1H)

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 $CHCl_3$ (1.5 mL) was added aldehyde (0.375 mmol, 5 eq.), and anhydrous

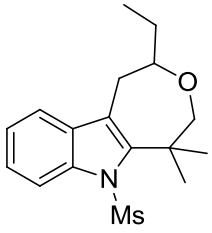
$ZnCl_2$ (0.113 mmol, 1.5 eq.). The reaction was stirred at room temperature for 24 h. The reaction mixture was added into ice-water and extracted with DCM for 3 times. The organic layers were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **44b ~ 53b**.



44b

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

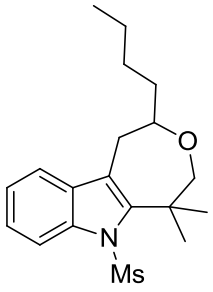
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 – 8.06 (m, 1H), 7.45 – 7.42 (m, 1H), 7.33 – 7.30 (m, 2H), 3.96 (d, J = 12.6 Hz, 1H), 3.81 (dd, J_1 = 11.7 Hz, J_2 = 6.3 Hz, 1H), 3.56 (d, J = 12.6 Hz, 1H), 2.94 (d, J = 6.3 Hz, 2H), 2.71 (s, 3H), 1.90 – 1.79 (m, 1H), 1.60 (s, 3H), 1.50 (s, 3H), 1.00 (dd, J_1 = 6.9 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).



45b

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

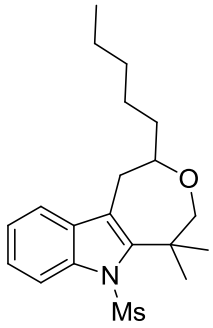
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 1H), 7.44 – 7.41 (m, 1H), 7.33 – 7.30 (m, 2H), 3.97 – 3.90 (m, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 3.58 (d, *J* = 12.6 Hz, 1H), 3.04 – 2.86 (m, 2H), 2.69 (s, 3H), 1.73 – 1.55 (m, 2H), 1.60 (s, 3H), 1.51 (s, 3H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 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 $C_{17}H_{24}NO_3S^+$ 322.1471, found 322.1485.



46b

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

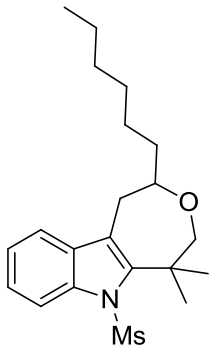
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 1H), 7.44 – 7.41 (m, 1H), 7.33 – 7.30 (m, 2H), 4.00 (m, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.03 – 2.86 (m, 2H), 2.69 (s, 3H), 1.75 – 1.32 (m, 6H), 1.60 (s, 3H), 1.50 (s, 3H), 0.92 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 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).



47b

5,5-Dimethyl-6-(methylsulfonyl)-2-pentyl-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-*b*]indole

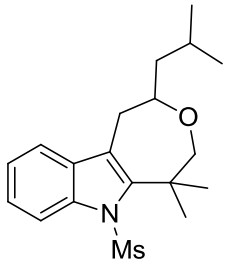
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 1H), 7.43 – 7.40 (m, 1H), 7.33 – 7.30 (m, 2H), 4.00 (m, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.03 – 2.86 (m, 2H), 2.69 (s, 3H), 1.73 – 1.32 (m, 8H), 1.60 (s, 3H), 1.50 (s, 3H), 0.90 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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).



48b

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

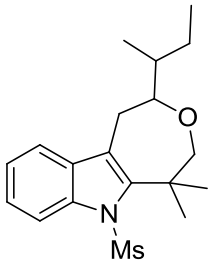
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 1H), 7.43 – 7.41 (m, 1H), 7.33 – 7.30 (m, 2H), 4.00 (m, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.03 – 2.86 (m, 2H), 2.69 (s, 3H), 1.75 – 1.26 (m, 10H), 1.60 (s, 3H), 1.50 (s, 3H), 0.87 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6 (C), 138.6 (C), 131.8 (C), 125.2 (CH), 124.3 (CH), 122.6 (C), 118.3 (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).



49b

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

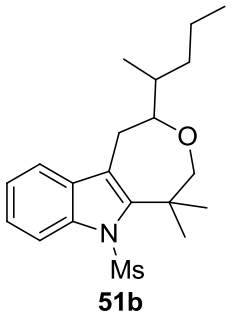
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 1H), 7.43 – 7.40 (m, 1H), 7.33 – 7.30 (m, 2H), 4.08 – 4.04 (m, 1H), 3.90 (d, *J* = 12.6 Hz, 1H), 3.55 (d, *J* = 12.6 Hz, 1H), 3.01 – 2.84 (m, 2H), 2.68 (s, 3H), 1.91 – 1.82 (m, 1H), 1.59 (s, 3H), 1.51 (s, 3H), 1.33 – 1.26 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.7 (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).



50b

2-(*sec*-Butyl)-5,5-dimethyl-6-(methylsulfonyl)-2,4,5,6-tetrahydro-1*H*-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).

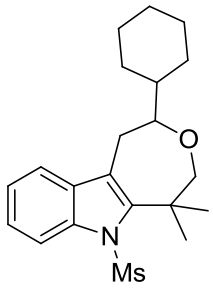


51b

5,5-Dimethyl-6-(methylsulfonyl)-2-(pentan-2-yl)-2,4,5,6-tetrahydro-1*H*-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

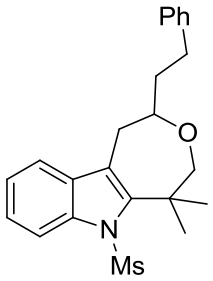
(s, 3H), 1.47 (s, 3H), 1.32 – 1.22 (m, 5H), 0.99 – 0.90 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.5 (C), 138.5 (C), 131.6 (C), 125.2 (CH), 124.3 (CH), 123.5 (C), 118.4 (CH), 116.4 (CH), 80.9 (CH), 78.2 (CH_2), 40.5 (C), 38.7 (CH), 37.6 (CH_3), 35.1 (CH_2), 25.7 (CH_2), 25.4 (CH_3), 24.1 (CH_3), 20.6 (CH_2), 14.8 (CH_3), 14.4 (CH_3).



52b

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

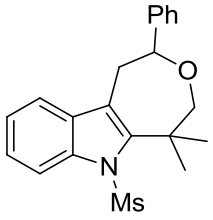
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 – 8.06 (m, 1H), 7.45 – 7.42 (m, 1H), 7.33 – 7.30 (m, 2H), 3.96 (d, J = 12.6 Hz, 1H), 3.80 (dd, J_1 = 12 Hz, J_2 = 6 Hz, 1H), 3.52 (d, J = 12.6 Hz, 1H), 2.95 (d, J = 6.6 Hz, 2H), 2.71 (s, 3H), 1.91 – 1.68 (m, 5H), 1.61 (s, 3H), 1.48 (s, 3H), 1.32 – 1.08 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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).



53b

5,5-Dimethyl-6-(methylsulfonyl)-2-phenethyl-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-*b*]indole

^{1}H NMR (300 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_2), 76.3 (CH), 40.6 (C), 38.3 (CH_2), 37.4 (CH_3), 31.7 (CH_2), 28.7 (CH_2), 25.0 (CH_3), 24.1 (CH_3).

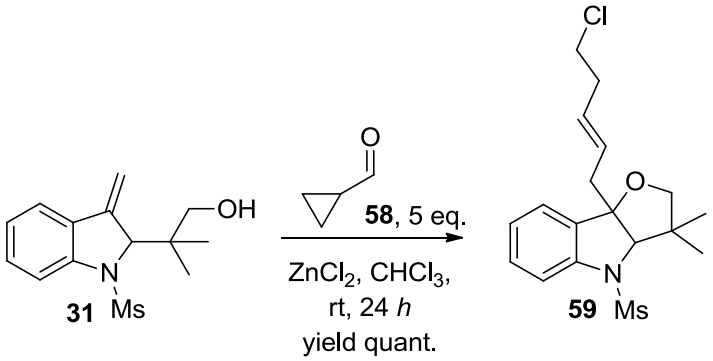


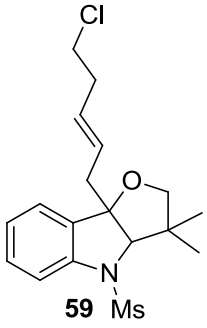
33b

5,5-Dimethyl-6-(methylsulfonyl)-2-phenyl-2,4,5,6-tetrahydro-1*H*-oxepino[4,5-*b*]indole

^{1}H NMR (300 MHz, $CDCl_3$): δ 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





(*E*)-8b-(4-Chlorobut-2-en-1-yl)-3,3-dimethyl-4-(methylsulfonyl)-3,3a,4,8b-tetrahydro-2*H*-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 μL, 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_2SO_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 $C_{18}H_{25}ClNO_3S^+$ 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.

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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**).[1] Compared to hydrogen, fluorine is much more electronegative but has a similar small size.[2] Incorporating fluorine atoms increases lipophilicity, improves its partitioning into membranes and hence increases bioavailability.[2,3] Moreover, the strong C-F bond resists deactivation in the liver by cytochrome P450 oxidases reducing drug metabolism.[4] Therefore, fluorine and fluorinated substituents are attractive bioisosteres.

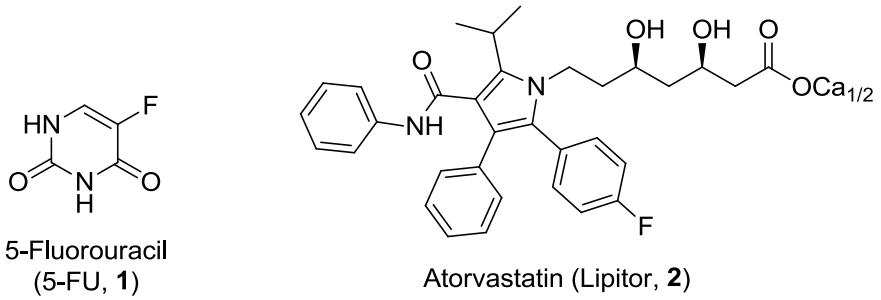


Figure 3.1.1 Examples of fluorinated drugs

Among various fluorinated substituents, fluoroalkene (C=CF) has been widely used as a replacement for the peptide bond in the field of medicinal chemistry.[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.

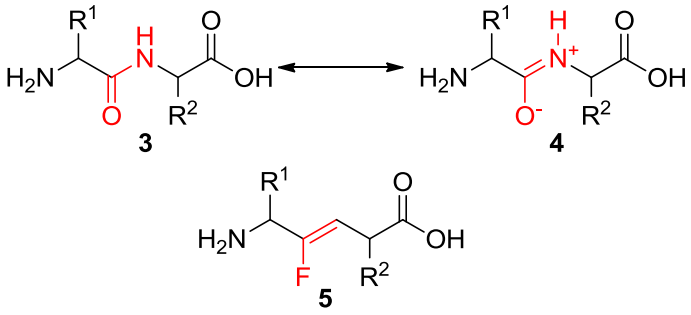
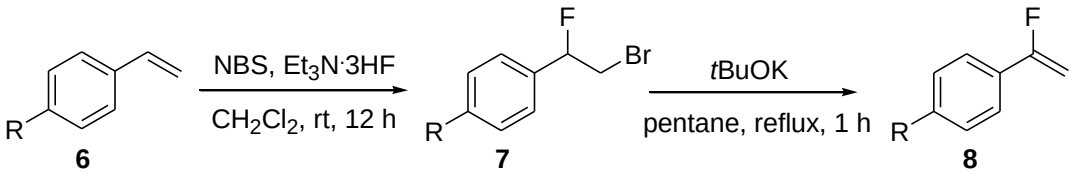


Figure 3.1.2 Dipeptide and its fluoroalkene bioisostere **5**

3.2 Research Design

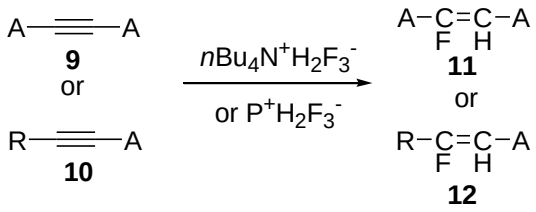
Fluoroalkenes are generally obtained in multi-step synthetic sequences.[6] For example, dihalide compound **7** is usually synthesized in advance to generate fluoroalkene **8** (Scheme 3.2.1).[7]



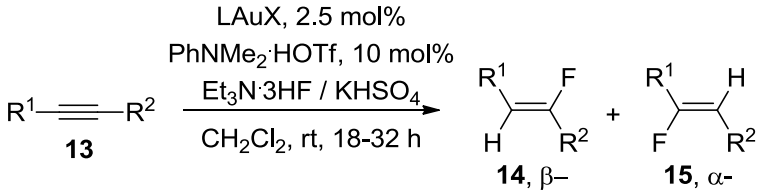
Scheme 3.2.1 Example of multi-step synthesis of fluoroalkene[7]

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 dihydrogentrifluoride reagents (Scheme 3.2.2).[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).[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.

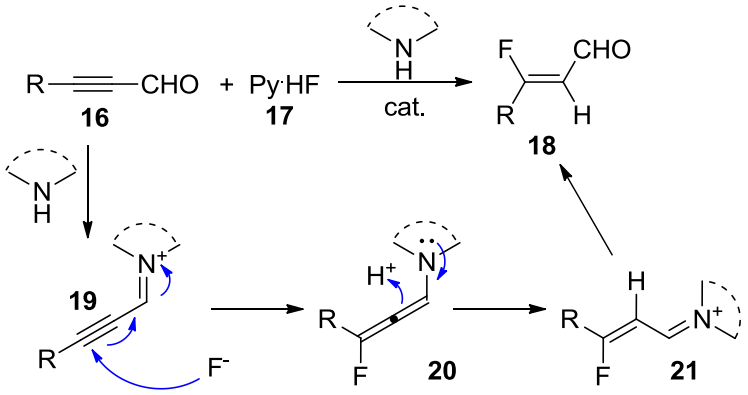


Scheme 3.2.2 HF addition to alkynes using $nBu_4N^+H_2F_3^-$ or $P^+H_2F_3^-$



Scheme 3.2.3 Au-catalyzed HF addition to alkynes

Recent studies from our group[10] and others[11] reveal that alkynals can be activated by a secondary amine catalyst via immium 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**.

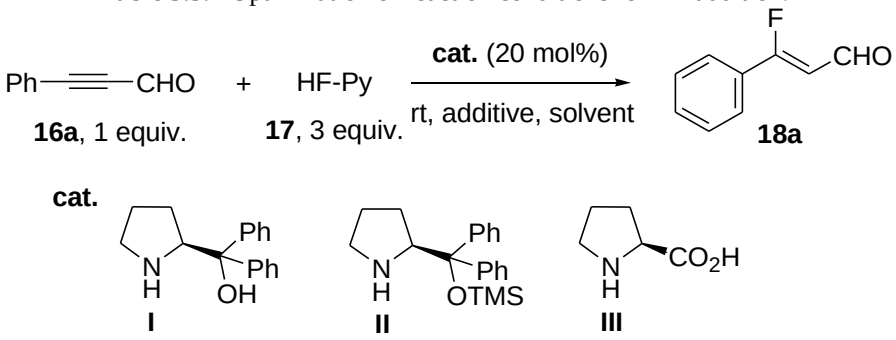


Scheme 3.2.4 Proposed secondary amine catalyzed HF addition to alkynals

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.[a]



Entry	Catalyst	Solvent	Additive	Time (h)	Conversion (%)	Yield (%)[b]
1	**I**	*t*-BuOMe	None	7	70	56
2	**II**	*t*-BuOMe	None	72	< 10	-
3	**III**	*t*-BuOMe	None	72	< 10	-
4	**I**	*t*-BuOMe	0.8 equiv. DABCO	24	100	decomposed
5	**I**	*t*-BuOMe	0.5 equiv. TEA	72	100	43
6	**I**	*t*-BuOMe	1.0 equiv. TEA	36	100	38

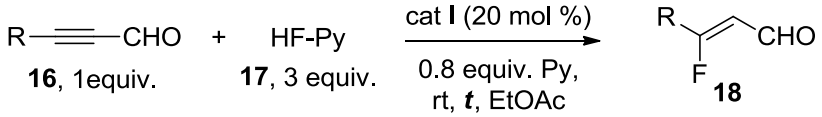
7	**I**	*t*-BuOMe	1.0 equiv. pyridine	24	100	45
8	**I**	*t*-BuOMe	0.5 equiv. $NaHCO_3$	72	< 10	-
9	**I**	*t*-BuOMe	1.2 equiv. Na_2CO_3	72	< 10	-
10	**I**	*t*-BuOMe	1.2 equiv. KOAc	72	< 10	-
11	**I**	Acetone	1.2 equiv. pyridine	72	100	17
12	**I**	CH_3CN	1.2 equiv. pyridine	72	100	30
13	**I**	EtOAc	1.2 equiv. pyridine	72	100	58
14	**I**	EtOAc	1.2 equiv. pyridine	4 h	100	58
15	**I**	EtOAc	1.0 equiv. pyridine	4 h	100	63
16	**I**	EtOAc	0.8 equiv. pyridine	1 h	100	82
17	**I**	EtOAc	0.5 equiv. pyridine	96 h	100	60

[a] The reactions were carried out on a 0.1-mmol scale of **16a** and monitored by appearance of **18a** by TLC and ^{1}H NMR spectroscopy. [b] 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).

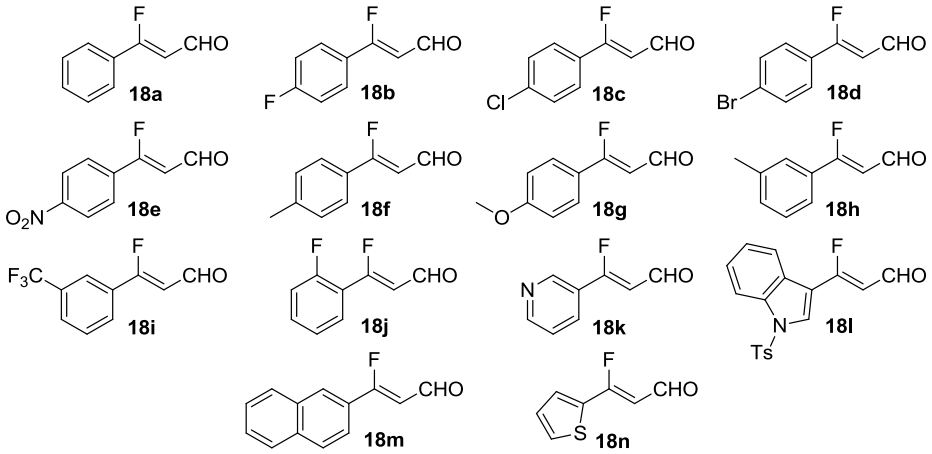
Having established the optimal conditions for HF addition, we examined the alkynal scope (Table 3.3.2). The reaction went smoothly with both electron-donating and electron-withdrawing substituents at *para*- and *meta*-position of benzene ring (Table 3.3.2, entries 1 to 8). However, when *ortho*-position 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[a]



Entry	Alkynal	R	*t* (h)	Product	Yield (%)[b]
1	**16b**	4-FC_6H_4	1	**18b**	80
2	**16c**	4-ClC_6H_4	1	**18c**	79
3	**16d**	4-BrC_6H_4	1	**18d**	75
4	**16e**	4-$NO_2C_6H_4$	1	**18e**	76
5	**16f**	4-MeC_6H_4	2	**18f**	68
6	**16g**	4-$OMeC_6H_4$	4	**18g**	63
7	**16h**	3-MeC_6H_4	2	**18h**	73
8	**16i**	3-$CF_3C_6H_4$	1	**18i**	78
9	**16j**	2-F C_6H_4	1	**18j**	16
10	**16k**	3-pyridinyl	1	**18k**	45
11	**16l**	N-Ts-3-indolyl	1.5	**18l**	66
12	**16m**	2-naphthalenyl	1	**18m**	66
13	**16n**	2-thiophenyl	2.5	**18n**	79

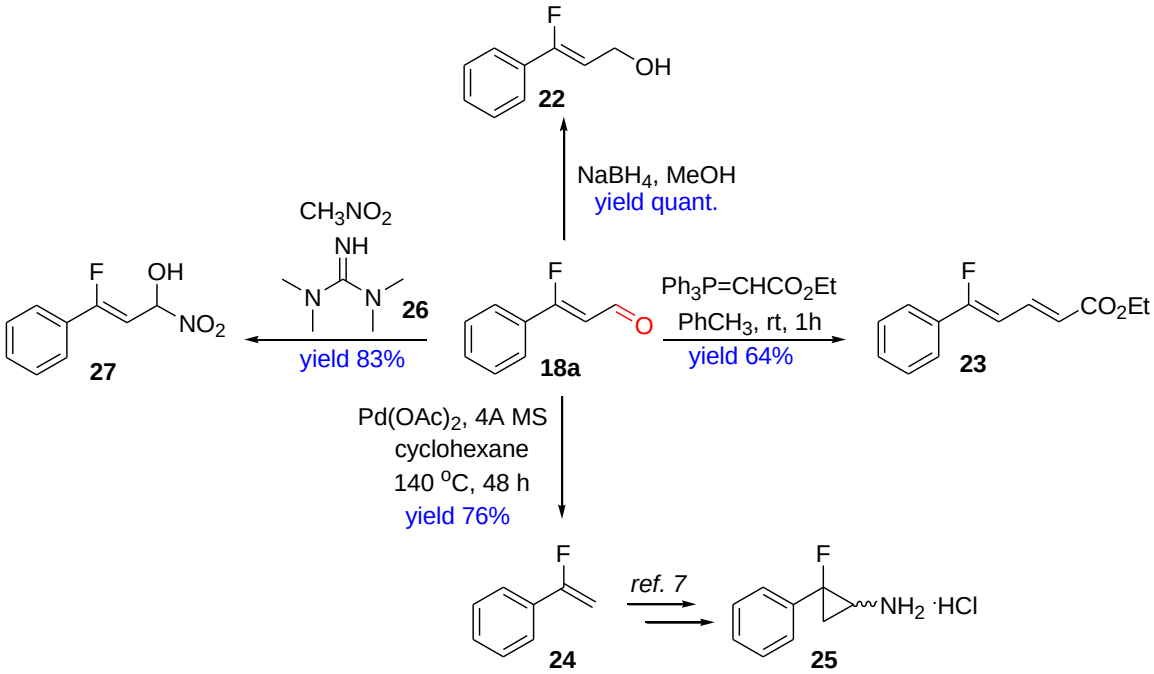
[a] The reactions were carried out on a 0.1-mmol scale of **16** and monitored by appearance of **18** by TLC and ^{1}HNMR spectroscopy. [b] Isolated yields.



3.4 Synthetic Applications

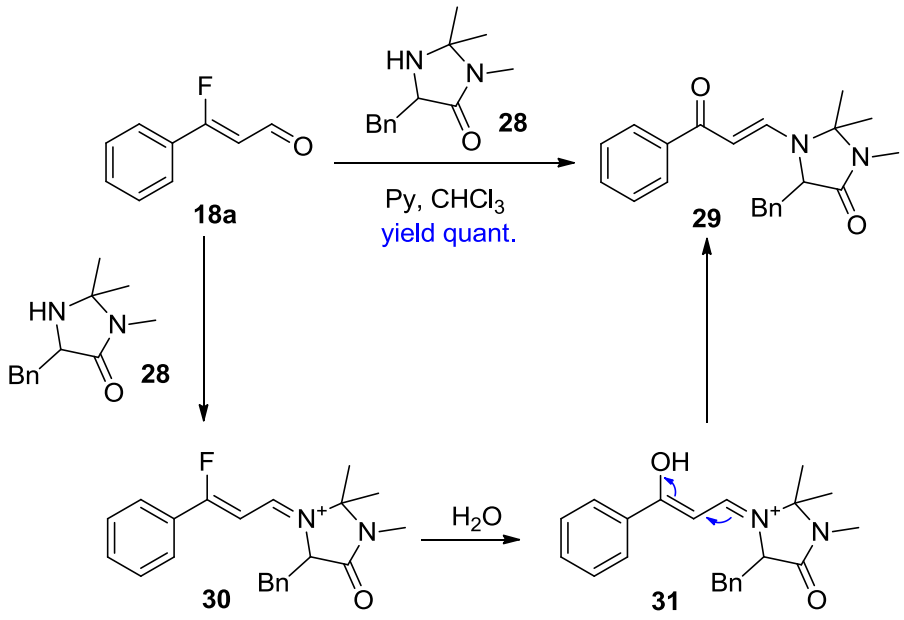
Our next focus was directed towards the utilization of *Z*-fluoroalkenes in the synthesis of new fluorinated compounds.

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 $NaBH_4$ 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.[7] The Henry reaction of β-fluoroenal **18a** with CH_3NO_2 under the base **26** generated compound **27** in a good yield.



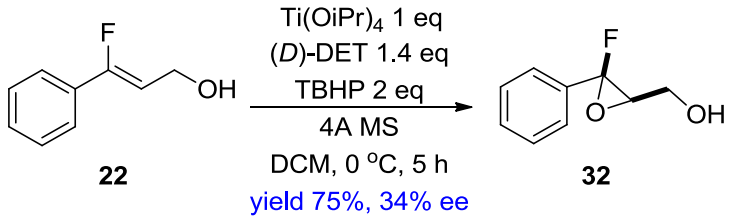
Scheme 3.4.1.2 Reaction of **18a** with **28**

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

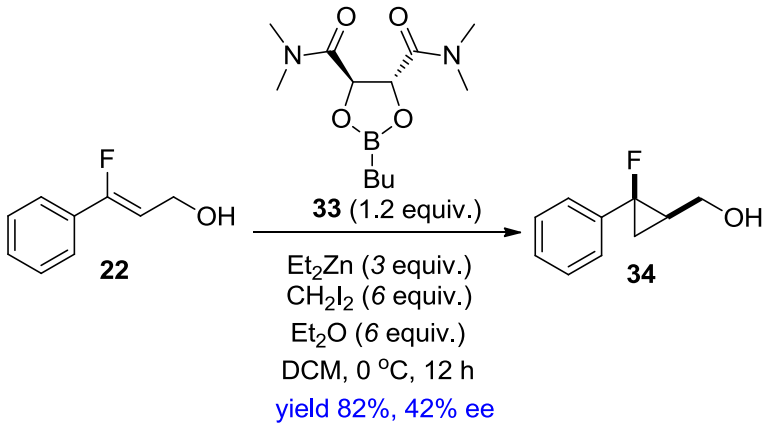
It is known that the C-F bond is the strongest single bond that carbon can form.[12] In general, the currently known functionalization processes of C−F bond often lose the fluorine atom.[13] Therefore, the functionalization of C−F bonds is a challenging task that has drawn much attention.

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).



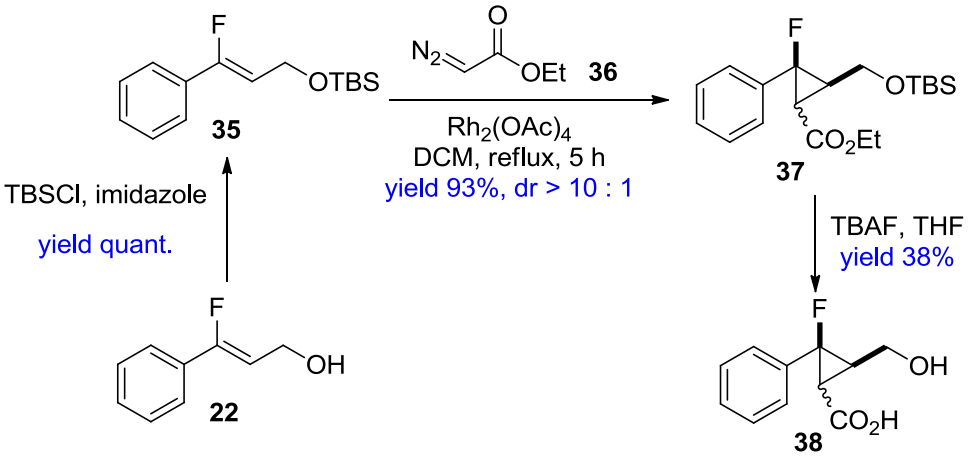
Scheme 3.4.2.1 Sharpless epoxidation of alcohol **22**

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.[14] However, limited studies have been carried out for their synthesis.[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).



Scheme 3.4.2.2 Simmons-Smith reaction of alcohol **22**

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.



Scheme 3.4.2.3 Preparation of monofluorocyclopropane (**37**) via ethyl diazoacetate (**36**)

3.5 Conclusions

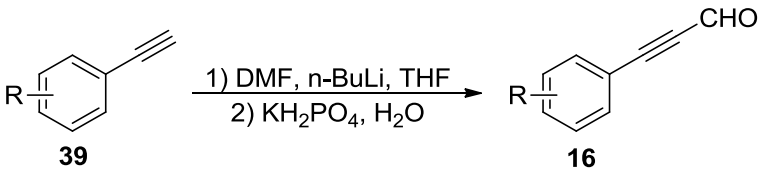
In summary, we have developed a novel highly efficient and stereoselective direct addition of F anion to alkynals catalyzed by a secondary amine. The β-fluoroenals are generated stereoselectively with *Z*-geometry. A variety of ynals can be applied for this conjugate addition process. Furthermore, we 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 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. $CDCl_3$ (δ = 7.26 and 77.0 for ^{1}H and ^{13}CNMR spectra respectively), DMSO-d6 (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.

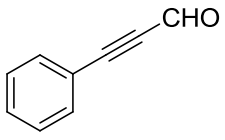
3.6.1 Preparation of alkynal substrates

3.6.1.1 Procedure for preparation of 16a and 16g



39 **16**

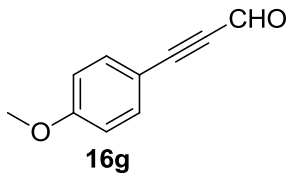
General Procedure: To a well-stirred solution of alkyne **39** (60 mmol) in anhydrous THF (150 mL) was added a solution of n-BuLi in hexanes (1.6 M, 41.3 mL, 66 mmol) at -40 ^{o}C. The reaction mixture was stirred 15 min at -40 ^{o}C, and then anhydrous DMF (9.3 mL, 120 mmol) was added in one portion. 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_2PO_4 (30 g, 220 mmol) in H_2O (270 mL) and EtOAc (300 mL) at 0 ^{o}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_2SO_4, and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **16**.



16a

3-Phenylpropiolaldehyde

^{1}H NMR (500 MHz, $CDCl_3$): δ 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).

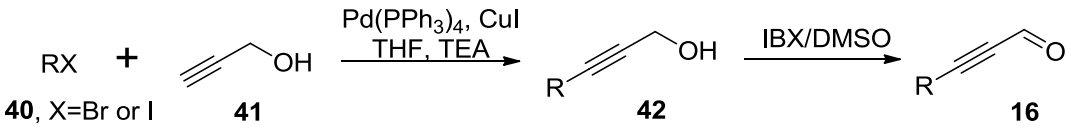


16g

3-(4-Methoxyphenyl)propiolaldehyde

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.40 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 3.86 (s, 3H).

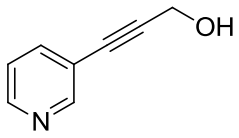
3.6.1.2 Procedure for preparation of 16k and 16n



40, X=Br or I **41** **42** **16**

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 μL, 4.8 mmol) and anhydrous THF (2 mL) was added propargyl alcohol (89 μL, 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**.

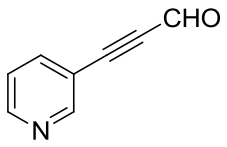
To a solution of alcohol **42** (0.75 mmol) in DMSO (1 mL) was added IBX (700 mg, 1.13 mmol). The reaction mixture was stirred at rt for 0.5 h, and then poured into ice-water, extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **16**.



42k

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

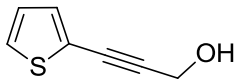
3-Bromo-pyridine was used as the starting material. The coupling reaction was stirred at 50 ^oC for 24 h. ^1H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.54 (d, J = 4.5 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.27-7.23 (m, 1H), 4.52 (d, J = 5.7 Hz), 2.05 (t, J = 5.7 Hz).



16k

3-(Pyridin-3-yl)propiolaldehyde

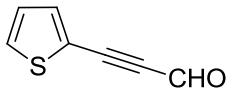
^1H NMR (300 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.84 (d, J = 1.2 Hz, 1H), 8.70 (dd, J_1 = 4.8 Hz, J_2 = 1.7 Hz, 1H), 7.90 (dt, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 7.37 (ddd, J_1 = 8.1 Hz, J_2 = 4.8 Hz, J_3 = 0.9 Hz, 1H).



42n

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).

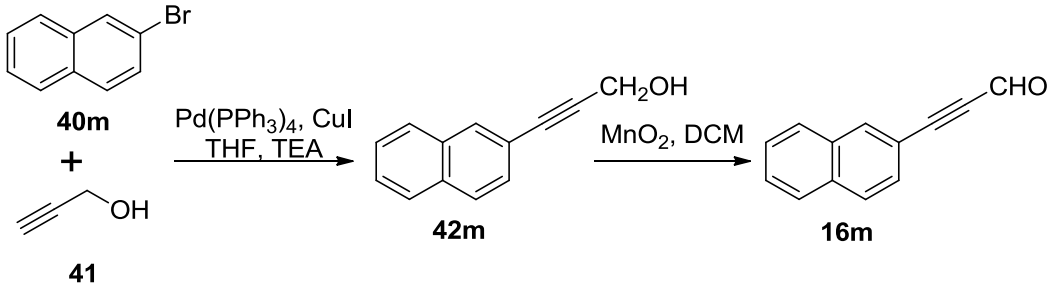


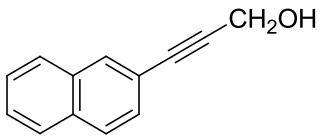
16n

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

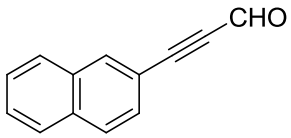




42m

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. ^{1}H 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).



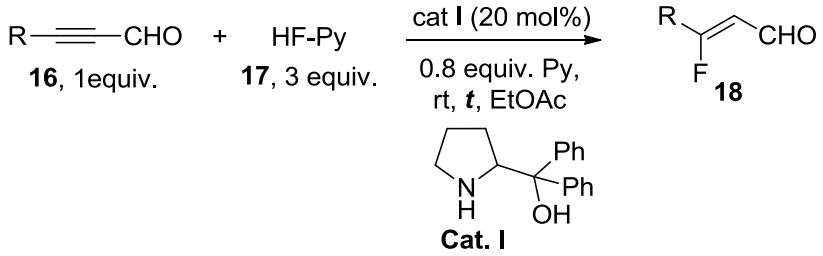
16m

3-(Naphthalen-2-yl)propiolaldehyde

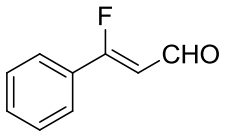
To a solution of alcohol **42m** (100 mg, 0.55 mmol) in DCM (2 mL) was added activated MnO_2 (530 mg, 5.5 mmol). The reaction mixture was stirred at rt for 4 h. The mixture was filtered through a Celite pad and the solvent was removed under reduced pressure. The residue was submitted to chromatography to afford alkynal **16m** (81 mg, 82%

yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 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 β-fluoroenals 18a-18m



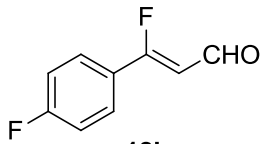
General Procedure: To a solution of alkynal **16** (0.1 mmol), pyridine (6.5 μL, 0.08 mmol) and cat. **I** (5.1 mg, 0.02 mmol) in EtOAc (1 mL) was added HF-Py **17** (7.8 μL, 0.3 mmol) at rt. The reaction mixture was stirred at rt for the time listed in Table 3.3.2. Then, the reaction mixture was poured into ice-water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **18**.



18a

(*Z*)-3-fluoro-3-phenylacrylaldehyde

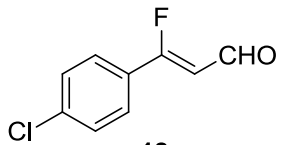
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 2H), 7.55-7.45 (m, 3H), 6.10 (dd, J_1 = 33.6 Hz, J_2 = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7 (d, *J* = 12.0 Hz, CH), 171.5 (d, *J* = 273.8 Hz, C), 132.5 (CH), 129.4 (d, *J* = 25.5 Hz, C), 129.1 (CH), 126.0 (d, *J* = 8.3 Hz, CH), 107.3 (d, *J* = 5.3 Hz, CH).



18b

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

^{1}H NMR (300 MHz, $CDCl_3$): δ 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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).

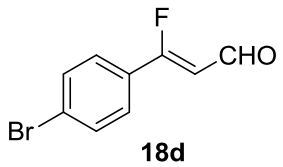


18c

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

^{1}H NMR (300 MHz, $CDCl_3$): δ 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). ^{13}C NMR (125 MHz,

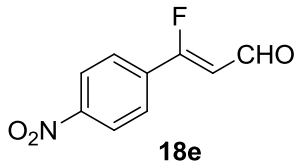
$CDCl_3$): δ 188.4 (d, *J* = 11.8 Hz, CH), 170.3 (d, *J* = 273.0 Hz, C), 138.8 (C), 129.5 (CH), 127.9 (d, *J* = 26.3 Hz, C), 127.2 (d, *J* = 8.3 Hz, CH), 107.5 (d, *J* = 5.3 Hz, CH).



18d

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

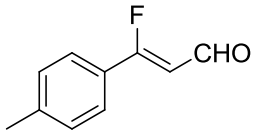
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.18 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.56 (dd, J_1 = 6.8 Hz, J_1 = 1.8 Hz, 2H), 6.08 (dd, J_1 = 34.0 Hz, J_2 = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 181.4 (d, *J* = 12.5 Hz, CH), 162.3 (d, *J* = 272.5 Hz, C), 125.4 (C, CH), 121.2 (d, *J* = 26.3 Hz, C), 120.2 (d, *J* = 7.5 Hz, CH), 100.5 (d, *J* = 3.8 Hz, CH).



18e

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

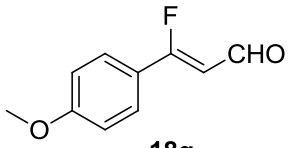
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.23 (d, *J* = 7.2 Hz, 1H), 8.34 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 9.0 Hz, 2H), 6.08 (dd, J_1 = 33.9 Hz, J_2 = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.0 (d, *J* = 11.3 Hz, CH), 168.5 (d, *J* = 273.3 Hz, C), 149.8 (C), 135.2 (d, *J* = 27.0 Hz, C), 126.9 (d, *J* = 8.0 Hz, CH), 124.3 (CH), 109.7 (d, *J* = 5.0 Hz, CH).



18f

(*Z*)-3-fluoro-3-(p-tolyl)acrylaldehyde

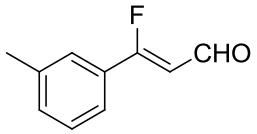
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.17 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.05 (dd, J_1 = 33.9 Hz, J_2 = 7.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.8 (d, *J* = 12.0 Hz, CH), 171.8 (d, *J* = 273.5 Hz, C), 143.4 (C), 129.8 (CH), 126.6 (d, *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).



18g

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

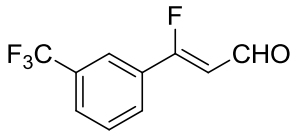
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.14 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.99 (dd, J_1 = 34.0 Hz, J_2 = 7.5 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.7 (d, *J* = 12.0 Hz, CH), 171.7 (d, *J* = 272.3 Hz, C), 163.1 (C), 128.0 (d, *J* = 9.0 Hz, CH), 121.6 (d, *J* = 25.5 Hz, C), 114.6 (CH), 105.7 (d, *J* = 4.5 Hz, CH), 55.5 (CH_3).



18h

(*Z*)-3-fluoro-3-(m-tolyl)acrylaldehyde

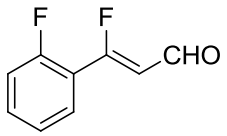
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.19 (d, *J* = 7.5 Hz, 1H), 7.51-7.49 (m, 2H), 7.40-7.35 (m, 2H), 6.08 (dd, J_1 = 33.6 Hz, J_2 = 7.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.8 (d, *J* = 11.6 Hz, CH), 171.8 (d, *J* = 274.1 Hz, C), 138.9 (C), 133.3 (CH), 129.3 (d, *J* = 25.9 Hz, C), 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).



18i

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

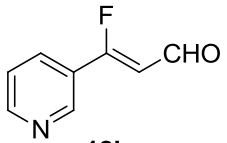
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.23 (d, *J* = 7.5 Hz, 1H), 7.95 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 6.16 (dd, J_1 = 33.6 Hz, J_2 = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2 (d, *J* = 11.6 Hz, CH), 169.6 (d, *J* = 273.4 Hz, C), 132.5, 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).



18j

(*Z*)-3-fluoro-3-(2-fluorophenyl)acrylaldehyde

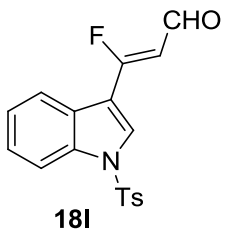
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.24 (dd, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 1H), 7.73 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.56-7.48 (m, 1H), 7.32-7.16 (m, 2H), 6.29 (dd, J_1 = 35.7 Hz, J_2 = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.0 (d, J = 13.3 Hz, CH), 166.1 (d, J = 270.0 Hz, C), 160.6 (dd, 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).



18k

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

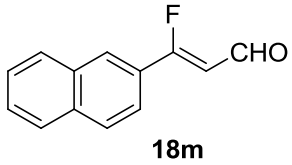
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.21 (d, J = 7.5 Hz, 1H), 8.96 (s, 1H), 8.76 (d, J = 4.2 Hz, 1H), 7.98 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.44 (dd, J_1 = 8.1 Hz, J_2 = 5.0 Hz, 1H), 6.14 (dd, J_1 = 33.9 Hz, J_2 = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.9 (d, J = 11.5 Hz, CH), 168.9 (d, 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).



18l

(*Z*)-3-fluoro-3-(1-tosyl-1H-indol-3-yl)acrylaldehyde

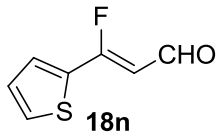
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.20 (d, *J* = 7.5 Hz, 1H), 8.14 (s, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.46-7.34 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.05 (dd, J_1 = 35.0 Hz, J_2 = 7.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2 (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).



18m

(*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).

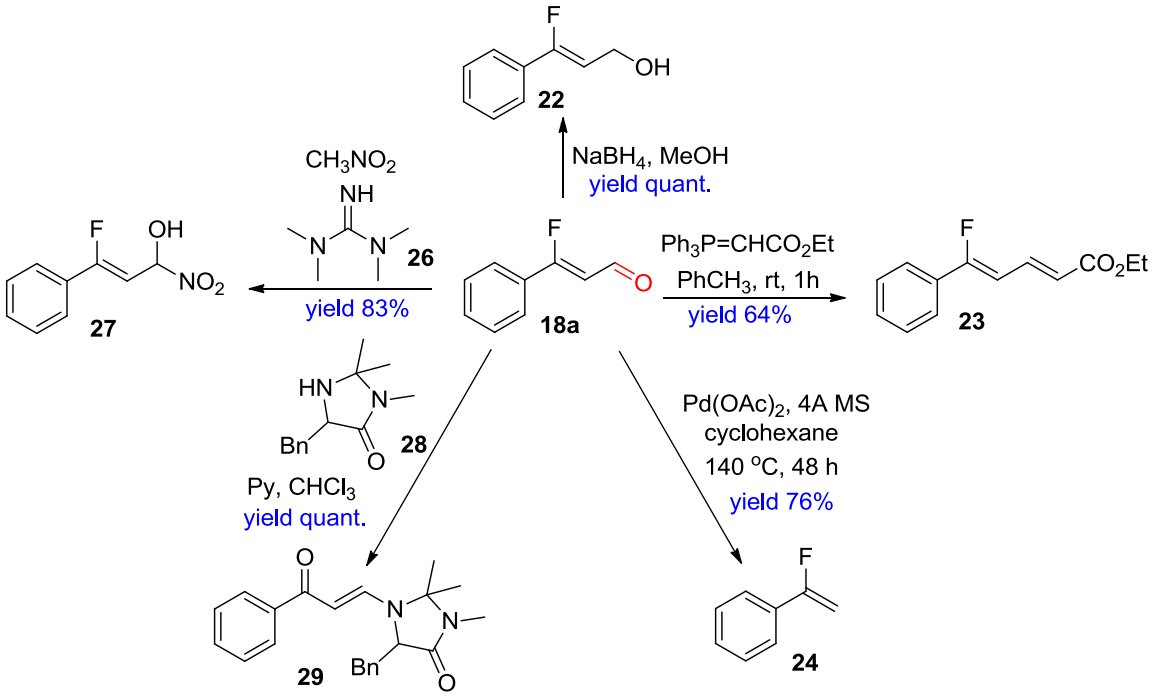


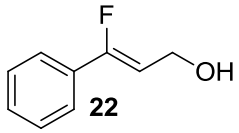
(*Z*)-3-fluoro-3-(thiophen-2-yl)acrylaldehyde

^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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

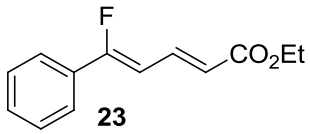




22

(*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 $NaBH_4$ (24 mg, 0.62 mmol) in some portions slowly within 30 min at 0 ℃. The reaction was stirred at rt for 30 min. Brine 10 mL was added and extrated with EtOAc for three times. The organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was submitted to chromatography to afford the alcohol **22** in 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.53 (m, 2H), 7.39-7.37 (m, 3H), 5.67 (dt, J_1 = 36.6 Hz, J_2 = 7.1 Hz, 1H), 4.45 (dd, J_1 = 7.1 Hz, J_2 = 2.0 Hz, 2H).

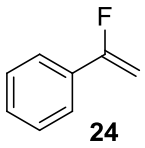


23

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

To a stirred solution of aldehyde **18a** (20.6 mg, 0.137 mmol) in $PhCH_3$ (1 mL) was added $Ph_3P{=}CHCO_2Et$ (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 Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford product **23** in 64% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77

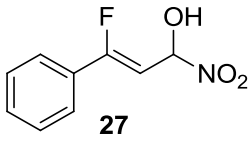
(dd, J_1 = 15.6 Hz, J_2 = 11.4 Hz, 1H), 7.63-7.60 (m, 2H), 7.42-7.40 (m, 3H), 6.22 (dd, J_1 = 33.3 Hz, J_2 = 11.4 Hz, 1H), 5.99 (d, J = 15.6 Hz, 1H), 4.24 (dd, J_1 = 14.3 Hz, J_2 = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 162.9, 159.4, 136.1, 136.0, 130.9, 130.6, 130.2, 128.6, 124.7, 124.6, 120.9, 120.8, 104.3, 104.1, 60.3, 14.2.



24

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 ^{o}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).

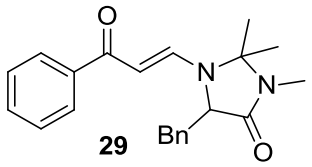


27

(*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_3NO_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_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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.



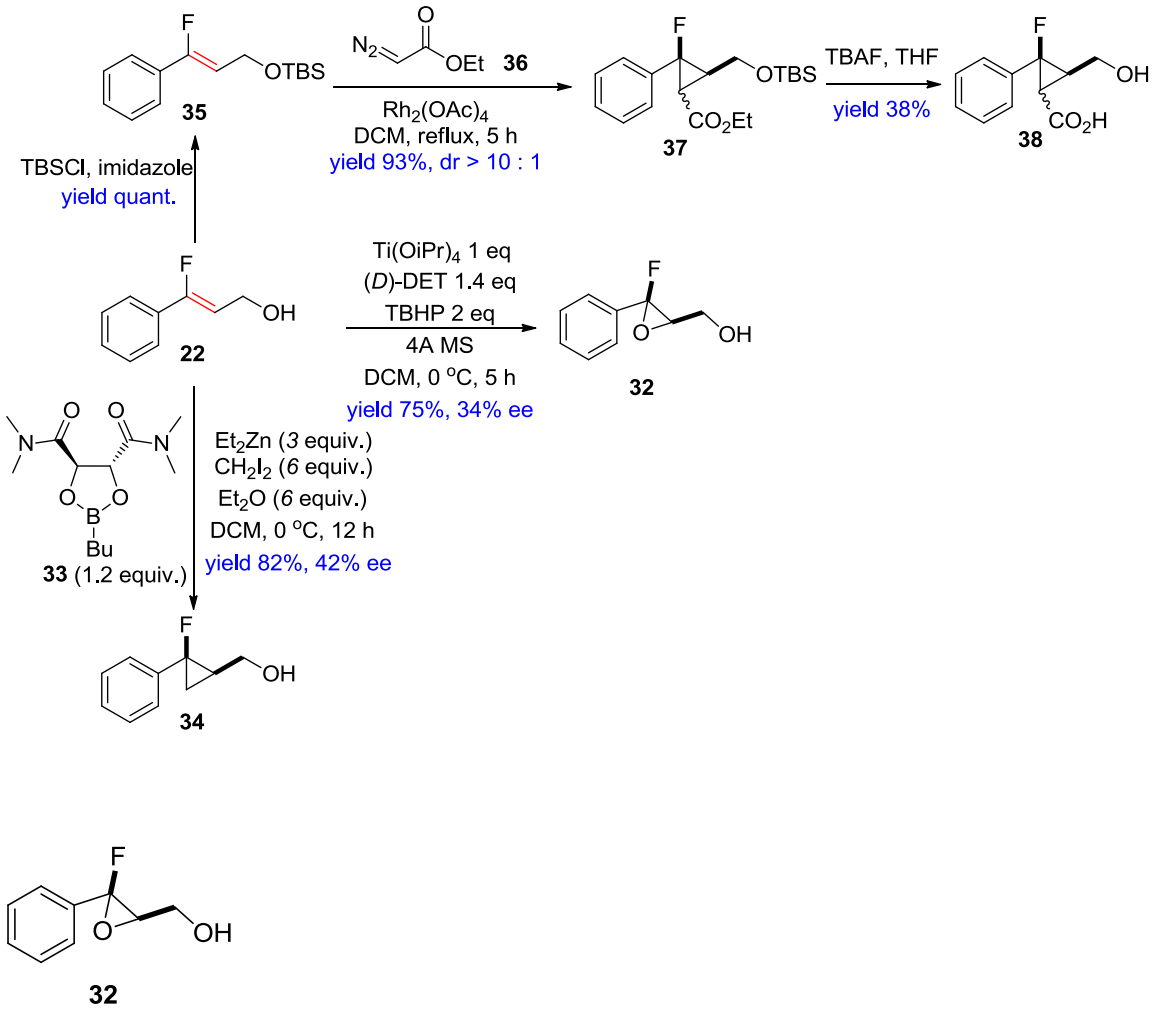
29

(*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 μL, 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_2SO_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, $CDCl_3$): δ 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), 2.72 (s, 3H), 1.45 (s, 3H), 0.57 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{22}H_{25}N_2O_2^+$ 349.1911, found 349.1920.

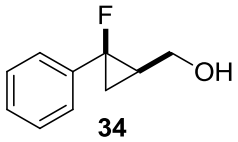
3.6.3.2 Reactions Based on C=C bond of 18a



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 ^{o}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 ^{o}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_2SO_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.

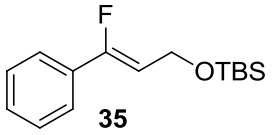


34

(2-Fluoro-2-phenylcyclopropyl)methanol

Et_2Zn (1M in hexanes, 300 μL, 0.3 mmol) and CH_2I_2 (47.7 μL, 0.6 mmol) were successively added to a mixture of anhydrous DCM (0.8 mL) and Et_2O (62.2 μL, 0.6 mmol) at -20 ^{o}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 ^{o}C and stirred for 12 h at this temperature. The reaction was quenched by adding a saturated NH_4Cl aqueous solution. The mixture was extracted with DCM. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4 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*). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.35 (m, 2H), 7.32-7.28 (m, 3H), 4.06 (ddd, J_1 = 11.7 Hz, J_2 = 5.9 Hz, J_3 = 1.2 Hz, 1H), 3.86-3.78 (m, 1H), 1.72-1.63 (m, 2H), 1.43-1.26 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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. ^{19}F NMR (282 MHz, $CDCl_3$): δ -191.9.

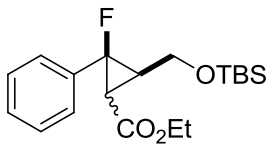


35

(*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 Na_2SO_4 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.51 (m, 2H),

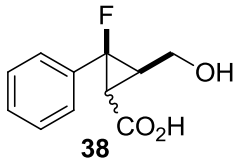
7.41-7.34 (m, 3H), 5.59 (dt, J_1 = 36.9 Hz, J_2 = 6.8 Hz, 1H), 4.50 (dd, J_1 = 6.8 Hz, J_2 = 2.3 Hz, 2H), 0.94 (s, 9H), 0.13 (s, 6H).



37

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 ^oC 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_2SO_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). ^1H 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.



38

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 ^{o}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 Na_2SO_4 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). ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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.

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List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
10-CSA	camphor-10-sufonic acid
Ac	acetyl
aq	aqueous
BINOL	1,1'-bi-2,2'-naphthol
Boc	*t*-butoxycarbonyl
calcd	calculated
cat.	catalyst
$CDCl_3$	deuterated chloroform
COSY	correlation spectroscopy
DABCO	1,4-diazabicyclo[2.2.2]octane
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
DET	diethyl tartrate
DFT	density functional theory
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
ESI	electron spray ionization
Et	ethyl
EtOAc	ethyl acetate
h	hour
IBX	*o*-iodoxybenzoic acid
i-Pr	*iso*-propyl
Me	methyl
mg	milligram
min	minute
mL	milliliter
MS	mass spectrometry
MS	molecular sieves
Ms	mesyl (methanesulfonyl)
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ph	phenyl
ppm	parts per million
PTC	phase transfer catalyst

Py	pyridine
quant.	quantitative
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS (TBDMS)	*t*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer Chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfony
W	watt
μL	microliter