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Mannich-Type Reaction of Aldimines with 2-Silyloxydienes Catalyzed by Ammonium Chloride

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Abstract

Reaction of imines with 2-silyloxydiene catalyzed by ammonium chloride has been perfectly proceeded under environmentally friendly conditions to give Mannich-type product selectively. The reaction would proceed via Mannich-type mechanism, not cyclization/ring-opening process. Cyclopropanation of the corresponding Mannich-type product gave the precursor of prasugrel skeleton in high yield.

Keywords

Mannich-Type Reaction, Ammonium Chloride, Imine, 2-Silyloxydiene

1. Introduction

Mannich-type reactions are widely recognized as a powerful method for constructing a variety of b-aminoketones [1]-[6]. However, Mannich-type reaction of imines with 2-silyloxydienes, which provides easy access to β-aminoketones having a terminal olefin, is still challenging because [4 + 2] type cycloadducts [7]-[15] or mixtures of Mannich-type products and cycloadducts [16] [17] [18] are obtained in most cases, as shown in **Figure 1**. Previously we first reported a highly effective Mannich-type reaction of imine with 2-silyloxydiene in the presence of zinc triflate and water [19] [20] [21] [22], which gave the corresponding β'-amino-α,β-enones as attractive skeletons for pharmaceutically useful compounds [23] [24] [25] [26]. Although many vinylogous Mannich-type reactions have been developed [27]-[36], only a few examples that describe the selective preparation of β'-amino-α,β-enones by the reaction of imine with 2-silyloxybutadiene have been reported so far. Thus, Kawęcki isolated the open-chain products from the aza-Diels-Alder reaction of sulfinimines with the

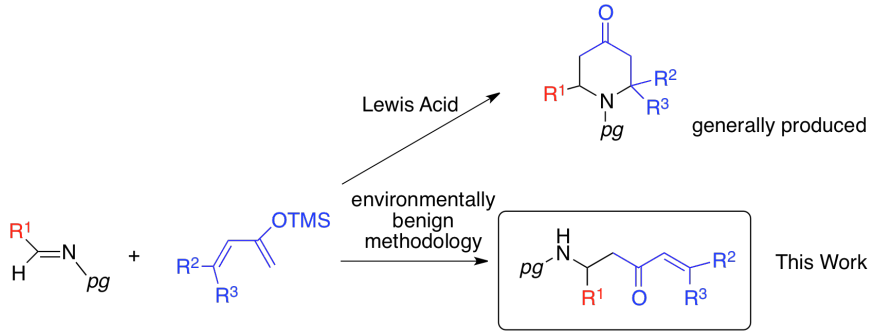


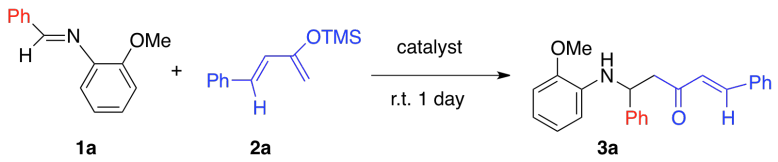
Figure 1. Reaction of imine with 2-silyloxydiene.

Rawal diene [37]. Pan *et al.* reported the addition of an α,β-unsaturated ketone-derived enolate to chiral *N*-phosphonyl imines [38], and Prasad *et al.* developed the reaction of chiral sulfinimines with silyloxydiene using TMSOTf [39]. In spite of these recent achievements, a more economical and environmentally benign synthetic methodology using green and sustainable catalysts has not been reported yet that offer alternatives to metal catalysts. Here we report the ammonium chloride-catalyzed Mannich-type reaction of imines with 2-silyloxybutadienes under mild conditions.

2. Results and Discussion

Initially, we examined the reaction of imine **1a**, derived from benzaldehyde and *o*-anisidine, with 2-silyloxybutadiene **2a** (Table 1). In contrast to the similar aza-Diels-Alder reaction of electron-rich Danishefsky's diene, reported by Ding et al., which afforded the cyclic product in MeOH in the absence of any acids [40], the reaction of imine **1a** with 2-silyloxybutadiene **2a** in EtOH or MeOH without additives gave no product (Table 1, entry 1). This result suggested that

Table 1. Mannich-type reacton of imine (**1a**) with 2-silyloxydiene (**2a**)[a].



1a **2a** **3a**

Entry	Catalyst	Solvent	Yield (%)[b]
1	none	EtOH	0
2	NH_4Cl	EtOH	95
3	NH_4Cl	CH_2Cl_2	0
4	NH_4Cl	ether	<20
5	NH_4Cl	toluene	<20
6	NaCl	EtOH	0
7	$[BMIM]^+ BF_4^+$	EtOH	0

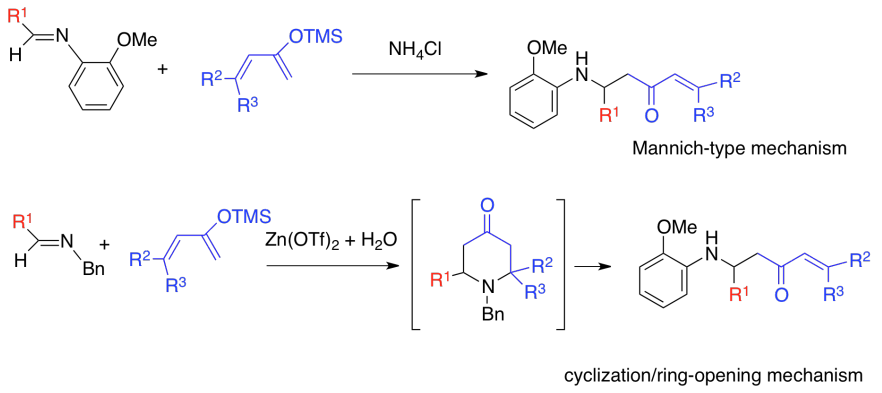
[a]Conditions: imine **1** (1 mmol), 2-silyloxydiene **2** (1.2 mmol), catalyst (0.1 mmol) in dry solvent (1 mL), r.t., 1 day. [b]Isolated yields.

using additive or catalyst was necessary to promote the reaction. We found that reaction with ammonium chloride (10 mol%) as a catalyst in EtOH gave the corresponding Mannich-type product **3a** selectively in 95% isolated yield (entry 2). Interestingly, no trace of cycloadduct was detected by 500 MHz ^{1}H NMR spectroscopy in the crude product. The previously reported reaction of imines having the *N*-benzyl group [19] did not give any products using ammonium chloride in EtOH, indicating that the reactivity of the imine is largely dependent on the *N*-protecting group. Finally, the attempt to perform the reaction using other additives and solvents was unsuccessful (Table 1, entries 3 - 7).

Having established the optimal reaction conditions for the Mannich-type reaction, we subsequently explored the scope of the reaction with respect to the imine substrates (Table 2). Imines **1b** and **1c** bearing an *o*- or *p*-tolyl group reacted to provide the corresponding products **3b** (90% yield) and **3c** (88% yield), respectively. Meanwhile, imines having an electron-donating or an electron-withdrawing group all reacted in a satisfactory way to provide the corresponding products **3d**-**3g** in high yield. The reaction with 2-silyloxybutadiene **2b**, derived from mesityl oxide, also proceeded to give **3h**-**3k** in 87% - 97% yields. Further investigation of the reaction with 2-silyloxydiene **2c** derived from acetylcyclohexene afforded the corresponding β'-amino-α,β-enones in 95% - 98% yields (Table 3).

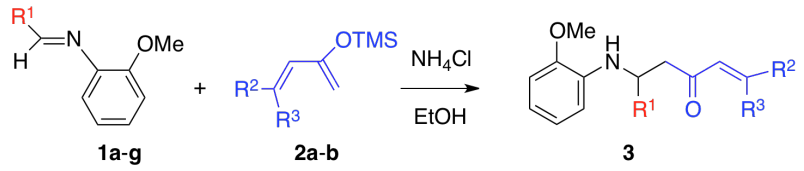
To investigate the reaction mechanism, the reaction of **1a** and **2a** was quenched after 1 h and analyzed using 500 MHz ^{1}H NMR spectroscopy. No cycloadduct was detected but a Mannich-type product and starting materials were observed. We suspect that the Mannich-type products are not formed via cyclization/ring-opening mechanism, as in the case of our previous reaction between *N*-benzyl-protected imine and 2-silyloxybutadiene using zinc triflate and water (Scheme 1) [19]. Additionally, further HCl work-up of the acyclic product **3a** gave no cycloadducts but the β'-amino-α,β-enone was recovered. However, *N*-benzyl-protected acyclic products afforded piperidones upon reaction with HCl [19], indicating that the acyclic product **3a** is stable under acidic conditions.

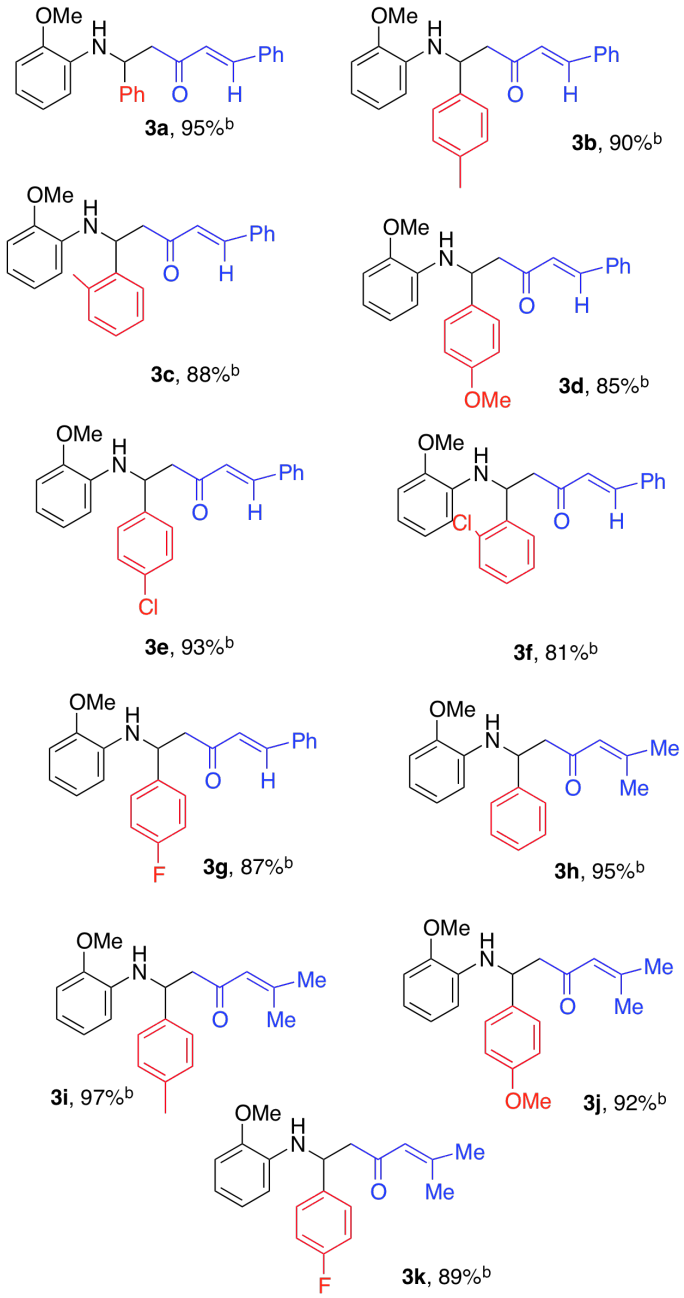
To demonstrate the synthetic utility of the Mannich-type products, we performed the preparation of a precursor of the prasugrel skeleton [41] [42], as



Scheme 1. Plausible mechanism.

Table 2. Scope of imines (**1**) and 2-silyloxydienes (**2a**)[a].

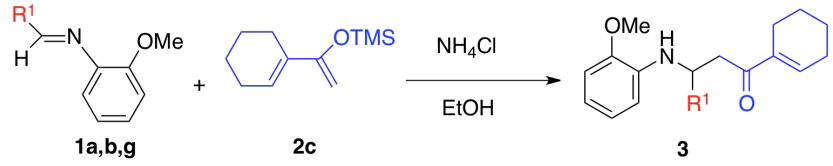


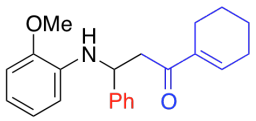


[a]Conditions: imine **1** (1 mmol), 2-silyloxydiene **2** (1.2 mmol), ammonium chloride (0.1 mmol) in dry EtOH (1 mL), r.t., 1 day. [b]Isolated yields.

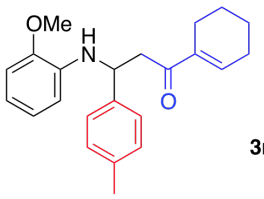
shown in Scheme 2. Thus, the reaction of the imine (**1h**) derived from *o*-fluorobenzaldehyde with 2-silyloxybutadiene **2b** proceeded smoothly to afford

Table 3. Reaction of imines (**1**) with 2-silyloxydiene (**2c**) derived from acetylcyclohexene[a].

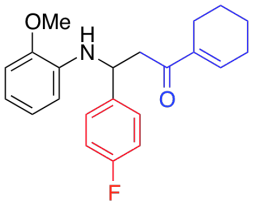




3l, 98%[b]



3m, 96%[b]



3n, 95%[b]

[a]Conditions: imine **1** (1 mmol), 2-silyloxydiene **2c** (1.2 mmol), ammonium chloride (0.1 mmol) in dry EtOH (1 mL), r.t., 1 day. [b]Isolated yields.

the corresponding acyclic product **3o**, which was then cyclopropanated to give **4o** in 65% yield.

3. Conclusion

In summary, a Mannich-type reaction of imine with 2-silyloxybutadiene that provides access to versatile β'-amino-α,β-enones has been developed under green conditions. We found that the use of ammonium chloride in EtOH is critical for the efficient outcome of the reaction, and this non-metal method is useful for various dienes and aldimines compared to reports so far [37] [38] [39]. According to our results, the reaction proceeds via Mannich-type mechanism, instead of through a cyclization/ring-opening process. Additionally, we prepared a precursor of the prasugrel skeleton by cyclopropanation of **3o**. Further investigation of the applicability of this reaction and mechanistic elucidation is currently in progress.

4. Experimental

Typical Procedure for Mannich-Type reaction of imine 1 with 2-silyloxydiene 2

To a stirred solution of NH_4Cl (0.006 g, 0.1 mmol), imine **1** (1 mmol) in dry ethanol (1 mL) was added 2-silyloxydiene **2** (1.2 mmol) at r.t.. The reaction mixture was stirred at r.t. for 24 h, the solvent was evaporated at reduced pressure.

The crude product was purified by flash column chromatography (ethyl acetate: *n*-hexane = 1:6) to afford **3**.

Data for **3a**; colorless oil, 0.34 g, 95%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.17 (dd, 1H, J = 15.4 Hz, 5.7 Hz), 3.23 (dd, 1H, J = 15.4 Hz, 7.5 Hz), 3.85 (s, 3H), 4.97 (dd, 1H, J = 6.9 Hz, 6.9 Hz), 6.44 (d, 1H, J = 7.5 Hz), 6.45 - 6.76 (m, 4H), 7.22 - 7.25 (m, 1H), 7.32 - 7.49 (m, 10H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{24}H_{23}NO_2$ 357.1729, found: 357.1727.

Data for **3b**; colorless oil. 0.30 g, 90%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.02 (s, 3H), 2.87 (dd, 1H, J = 15.4 Hz, 5.9 Hz), 2.95 (dd, 1H, J = 15.4 Hz, 6.9 Hz), 3.54 (s, 3H), 4.69 (dd, 1H, J = 6.6 Hz, 6.6 Hz), 6.23 (d, 1H, J = 6.9 Hz), 6.35 - 6.51 (m, 4H), 6.78 - 6.87 (m, 2H), 7.04 - 7.24 (m, 8H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{25}H_{25}NO_2$ 371.1885, found: 371.1894.

Data for **3c**; colorless oil. 0.32 g, 88%. ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.06 (s, 3H), 2.92 (dd, 1H, J = 15.4 Hz, 5.9 Hz), 2.96 (dd, 1H, J = 15.4 Hz, 7.0 Hz), 3.58 (s, 3H), 4.67 (dd, 1H, J = 6.3 Hz, 6.3 Hz), 6.23 (d, 1H, J = 7.7 Hz), 6.35 - 6.51 (m, 3H), 6.78 - 6.85 (m, 1H), 6.87 - 7.07 (m, 4H), 7.08 - 7.18 (m, 2H), 7.20 - 7.26 (m, 3H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{25}H_{25}NO_2$ 371.1885, found: 371.1902.

Data for **3d**; colorless oil. 0.32 g, 85%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.12 (dd, 1H, J = 15.5 Hz, 5.7 Hz), 3.20 (dd, 1H, J = 15.5 Hz, 6.9 Hz), 3.74 (s, 3H), 3.83 (s, 3H), 4.91 (dd, 1H, J = 6.3 Hz, 6.3 Hz), 6.46 (d, 1H, J = 1.7 Hz), 6.61 - 6.63 (m, 4H), 6.81 - 6.85 (m, 2H), 7.25 - 7.37 (m, 5H), 7.42 - 7.47 (m, 3H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{25}H_{25}NO_3$ 387.1834, found: 387.1838.

Data for **3e**; colorless oil. 0.36 g, 93%. ^{1}H NMR ($CDCl_3$, 300MHz) δ 3.12 (dd, 1H, J = 15.7 Hz, 5.5 Hz), 3.20 (dd, 1H, J =15.7 Hz, 5.5 Hz), 3.85 (s, 3H), 4.93 - 4.99 (m, 2H), 6.36 (d, 1H, J = 6.2 Hz), 6.61 - 6.76 (m, 4H), 7.26 - 7.53 (m, 10H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{24}H_{22}NO_2Cl$ 391.1339, found: 391.1328.

Data for **3f**; colorless oil. 0.32 g, 81%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.02 (dd, 1H, J = 14.9 Hz, 8.6 Hz), 3.28 (d, 1H, J = 3.5 Hz), 3.71 (s, 3H), 5.28 (dd, 1H, J = 9.1 Hz, 3.4 Hz), 6.21 (dd, 1H, J = 6.2 Hz, 1.8 Hz), 6.59 - 6.74 (m, 4H), 7.17 - 7.59 (m, 10H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{24}H_{22}NO_2Cl$ 391.1339, found: 391.1335.

Data for **3g**; colorless oil. 0.33 g, 87%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.13 (dd, 1H, J = 15.5 Hz, 5.7 Hz), 3.20 (dd, 1H, J = 15.5 Hz, 5.7 Hz), 3.83 (s, 3H), 4.93 (dd, 1H, J = 6.3 Hz, 6.3 Hz), 6.35 - 6.39 (m, 1H), 6.59 - 6.80 (m, 4H), 6.95 - 6.99 (m, 2H), 7.18 - 7.25 (m, 3H), 7.33 - 7.38 (m, 3H), 7.45 - 7.53 (m, 2H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{24}H_{22}NO_2$ 375.1634, found: 375.1628.

Data for **3h**; colorless oil. 0.29 g, 95%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.72 (s, 3H), 2.00 (s, 3H), 2.76 (dd, 1H, J = 16.9 Hz, 5.9 Hz), 2.82 (dd, 1H, J = 16.9 Hz, 5.9 Hz), 3.81 (s, 3H), 4.77 (dd, 1H, J = 6.6 Hz, 6.6 Hz), 5.91 (brs, 1H), 6.30 - 6.35 (m, 1H), 6.45 - 6.55 (m, 1H), 6.58 - 6.64 (m, 2H), 7.06 - 7.15 (m, 1H), 7.17 - 7.20 (m, 2H), 7.26 - 7.28 (m, 2H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{20}H_{23}NO_2$ 309.1729, found: 309.1722.

Data for **3i**; colorless oil. 0.31 g, 97%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (s, 3H), 2.11 (s, 3H), 2.30 (s, 3H), 2.90 (dd, 1H, J = 13.2 Hz, 5.7 Hz), 2.93 (dd, 1H, J

= 13.2 Hz, 5.7 Hz), 3.85 (s, 3H), 4.85 (dd, 1H, *J* = 6.9 Hz, 6.9 Hz), 6.04 (brs, 1H), 6.44 - 6.50 (m, 1H), 6.58 - 6.52 (m, 1H), 6.55 - 6.73 (m, 2H), 7.10 - 7.13 (m, 2H), 7.20 - 7.28 (m, 2H); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{21}H_{24}NO_2$ 323.1885, found: 323.1894.

Data for **3j**; colorless oil. 0.31 g, 92%. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 2.08 (s, 3H), 2.80 (dd, 1H, *J* = 15.4 Hz, 6.2 Hz), 2.90 (dd, 1H, *J* = 15.4 Hz, 6.2 Hz), 3.70 (s, 3H), 3.80 (s, 3H), 4.81 (dd, 1H, *J* = 6.6 Hz, 6.6 Hz), 5.95 - 6.00 (m, 1H), 6.34 - 6.44 (m, 1H), 6.52 - 6.58 (m, 1H), 6.67 - 6.72 (m, 2H), 6.79 - 6.84 (m, 2H), 7.24 - 7.28 (m, 2H); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{21}H_{25}NO_3$ 339.1834, found: 339.1836.

Data for **3k**; colorless oil. 0.29 g, 89%. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 3H), 2.10 (s, 3H), 2.88 (dd, 1H, *J* = 15.4 Hz, 5.9 Hz), 2.92 (dd, 1H, *J* = 15.4 Hz, 5.9 Hz), 3.11 (s, 3H), 4.84 (dd, 1H, *J* = 6.6 Hz, 6.6 Hz), 5.99 - 6.01 (m, 1H), 6.36 (d, 1H, *J* = 7.7 Hz), 6.59 - 6.76 (m, 3H), 6.95 - 7.01 (m, 2H), 7.32 - 7.37 (m, 2H); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{20}H_{22}NO_2F$ 327.1635, found: 327.1628.

Data for **3l**; colorless oil. 0.33 g, 98%. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 - 1.65 (m, 4H), 2.15 - 2.28 (m, 4H), 3.12 (d, 2H, *J* = 6.6 Hz), 3.85 (s, 3H), 4.82 - 4.90 (m, 1H), 4.92 - 5.05 (m, 1H), 6.37 (dd, 1H, *J* = 5.9 Hz, 1.8 Hz), 6.57 - 6.84 (m, 4H), 7.18 - 7.39 (m, 5H); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{22}H_{25}NO_2$ 335.1885, found: 335.1876.

Data for **3m**; colorless oil. 0.27 g, 78%. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 - 1.65 (m, 4H), 2.15 - 2.25 (m, 4H), 2.30 (s, 3H), 3.11 (d, 2H, *J* = 6.6 Hz), 3.85 (s, 3H), 4.82 (dd, 1H, *J* = 6.6 Hz, 6.6 Hz), 6.40 (d, 1H, *J* = 6.2 Hz), 6.57 - 6.75 (m, 3H), 6.83 - 6.86 (m, 1H), 7.10 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.4 Hz); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{23}H_{27}NO_2$ 349.2042, found: 349.2044.

Data for **3n**; colorless oil. 0.34 g, 95%. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.56 - 1.59 (m, 4H), 2.17 - 2.21 (m, 4H), 3.11 (dd, 2H, *J* = 5.9 Hz, 1.8 Hz), 3.86 (s, 3H), 4.80 - 4.87 (m, 1H), 4.96 (brs, 1H), 6.33 (dd, 1H, *J* = 7.7 Hz, 1.5 Hz), 6.59 - 6.77 (m, 3H), 6.82 - 6.87 (m, 1H), 6.93 - 7.02 (m, 2H), 7.33 - 7.37 (m, 2H); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{22}H_{24}NO_2F$ 353.1791, found: 353.1797.

Data for **3o**; colorless oil. 0.24 g, 97%. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.85 (s, 3H), 2.09 (s, 3H), 2.92 (dd, 1H, *J* = 15.4 Hz, 7.7 Hz), 2.97 (dd, 1H, *J* = 15.4 Hz, 7.7 Hz), 3.86 (s, 3H), 5.14 - 5.18 (m, 1H), 6.06 - 6.07 (m, 1H), 6.40 - 6.45 (m, 1H), 6.58 - 6.65 (m, 1H), 6.68 - 6.80 (m, 2H), 7.00 - 7.08 (m, 2H), 7.17 - 7.25 (m, 1H), 7.35 - 7.37 (m, 1H); HRMS (EI) *m*/*z* $[M]^+$ calcd. for $C_{20}H_{22}NO_2F$ 327.1635, found: 327.1637.

Cyclopropanation of 3o using trimethyloxosulfonium iodide

To a stirred solution of **3o** (0.243 g, 0.74 mmol) in DMSO (1 mL) was added trimethyloxosulfonium iodide (0.22 g, 1.0 mmol) and NaH (0.024 g, 1.0 mmol) at r.t. The mixture was stirred for 1 day and quenched with ice-water (20 mL). The mixture was extracted with ether, washed twice with water, and the organic layers were dried by Na_2SO_4. The solvent was removed at reduced pressure to give the product **4o** as a white solid (0.21g, 65%).

Data for **4o**; ^{1}H NMR($CDCl_3$, 500MHz) δ 0.71 - 0.72 (m, 1H), 0.86 (s, 3H), 1.06 (s, 3H), 1.15 - 1.16 (m, 1H), 1.75 - 1.80 (m, 1H), 3.06 (dd, 1H, J = 16.1 Hz, 5.7 Hz), 3.09 (dd, 1H, J = 16.1 Hz, 5.7 Hz), 3.77 (s, 3H), 5.08 (brs, 1H), 5.16 (dd, 1H, J = 6.3 Hz, 6.3 Hz), 6.40 - 6.42 (m, 1H), 6.60 - 6.65 (m, 1H), 6.71 - 6.74 (m, 2H), 7.01 - 7.05 (m, 2H), 7.17 - 7.25 (m, 1H), 7.36 - 7.37 (m, 1H); HRMS (EI) m/z $[M]^+$ calcd. for $C_{21}H_{24}NO_2F$ 341.1791, found: 341.1796.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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