

Cyclopropanation of Various Substrates *via* Simmons-Smith and Michael-Initiated Ring Closure (MIRC) Reactions

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ABSTRACT

Cyclopropanation of various electron rich and electron deficient olefins *via* Simmons-Smith and Michael-initiated ring closure reactions was studied in our research. Cinnamyl alcohol **18** was successfully cyclopropanated in a good to excellent yield using Simmons-Smith reactions. Methyl and benzyl crotonate **14** and **16** were labile in MIRC reaction condition indicated by the detection of starting material degradation in the NMR spectra of the crude reactions, and allowed a low to moderate product yield. The other starting materials, i.e., cinnamaldehyde **19**, methyl cinnamate **20**, mono- and di-protected cross-coupled product (4*R*,5*R*,*E*)-methyl-5-(*tert*-butyldimethylsilyloxy)-4-hydroxyhepta-2,6-dienoate **25** and (4*R*,5*R*,*E*)-methyl-5-(*tert*-butyldimethylsilyloxy)-4-(methoxymethoxy)-hepta-2,6-dienoate **26**, were apparently incompatible to the reaction condition set in our study.

Keywords: cyclopropanation, Michael-initiated ring closure, Simmons-Smith reaction

INTRODUCTION

The cyclopropyl unit is largely found in a numerous biologically active natural products and pharmaceuticals [1,2]. It is quite interesting due to its intrinsic instability related to the simplest carbocyclic ring bearing on it. The *sp*²-like character of the cyclopropane carbons accounts for its tendency to react in the most reactions associated with alkenes [3]. The cooperation of both ring strain and unusual bonding orbitals results in unique reactivity that has motivated to their use as synthetic intermediates and mechanistic probes [5].

The importance of the cyclopropane moiety has been reported by many authors. Some are exemplified in Figure 1 by the natural immunosuppressant and antibacterial belactosin A 1 and alkoxypropane 2 [5,6], a potential inhibitor of PDE4 which is an isozyme presents abundantly in inflammatory and immune cells. The other interesting compounds, which contain cyclopropane unit have recently been isolated by Deng's and Suárez-Ortiz' groups from the whole part of *Hyptis brevipes* plant. These 5,6-dihydro- α -pyrone derivatives, namely brevipolide A-J (compound 3–12), exhibited moderate cytotoxicity against a variety of tumor cell lines ($ED_{50} < 10 \mu M$) and were identified as inhibitors of the chemokine receptor CCR5 so that they are also potential candidates for treating human immunodeficiency virus (HIV) [7,8]. One of the synthetic version of these natural products, *ent*-brevipolide H 13, first prepared by Hou's group was also known and showed better

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activity (IC_{50} 7.7 μ M) against the cell proliferation of the human hormone-refractory prostate cancer cell line (PC-3) than the natural brevipolide H [9].

The valuable properties of the cyclopropyl unit have led to the development of many important methods for their preparation [4]. The two most common paths to provide this functionality involve the cyclopropanation of olefin using Simmons-Smith and Michael-initiated ring closure (MIRC) reactions [10,11]. Due to the significant value of this moiety, we performed cyclopropanation of various substrates in our research *via* those two reactions and reported the results here.

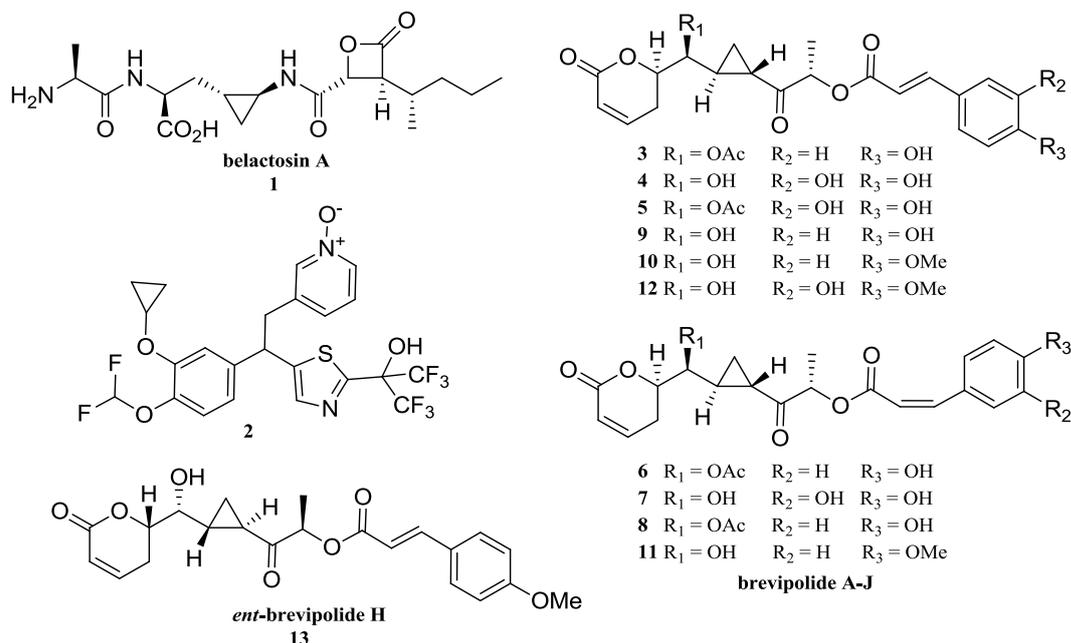


Figure 1. Cyclopropyl moiety in biologically active natural products and pharmaceuticals

EXPERIMENT

Chemicals and instrumentation

Chemicals used were analytical and synthetic grade: potassium carbonate (Showa), benzyl alcohol (Tedia), dichloromethane (Echo), 4-(dimethylamino)pyridine (Sigma Aldrich), crotonyl chloride (Alfa Aesar), sodium hydrogen carbonate (Scharlan), diethyl ether (Echo), sodium sulfate (Showa), cinnamaldehyde (Acros), ethanol (Acros), sodium borohydride (Riedel), copper (I) iodide (Fluka), methyl acrylate (Fluka), Grubbs' catalyst second generation (Sigma Aldrich), ethyl acetate (Echo), *n*-hexane (Echo), chloromethyl methyl ether, diisopropylethylamine (Fluka), sodium hydride (60% dispersion in mineral oil) (Acros), dimethylformamide (Fisher), trimethylsulfoxonium iodide (Sigma Aldrich), hydrochloric acid (Fisher), dimethyl sulfoxide (Scharlan), tetrahydrofuran (Tedia), diethyl zinc (1 M in *n*-hexane solution) (Sigma Aldrich), diiodomethane (Acros), chloroform-D (Sigma Aldrich), trifluoroacetic acid (Riedel), TiCl₄ (Showa), potassium hydride (Acros). The instrumentations used were NMR spectrometer 200 MHz and 300 MHz from Bruker.

Preparation of Benzyl Crotonate (16)

Potassium carbonate (3.3 g, 24 mmol) was added to a sealed 100 mL round bottom flask containing the mixture of benzyl alcohol (1.25 mL, 12 mmol) and dry dichloromethane (24

mL), followed by 4-(dimethylamino)pyridine (146 mg, 1.2 mmol) while stirring. Crotonyl chloride (3.45 mL, 36 mmol) was then added using micro syringe. The reaction mixture was refluxed for overnight, quenched with saturated NaHCO₃ solution and diluted with diethyl ether. The aqueous layer was further extracted with diethyl ether (3 x 50 mL) and the combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂) to give **16** (2.312 g, 12 mmol, ~100%). ¹H NMR (200 MHz, CDCl₃, 25 °C): δ = 7.40 (s, 5H), 7.20-6.90 (m, 1H), 5.93-5.80 (d, 1H), 2.01-1.80 (s, 3H) ppm.

Preparation of Cinnamyl Alcohol (18)

To a solution of cinnamaldehyde (2 g, 15.13 mmol) in 14 mL of 95% ethanol in a sealed 50 mL round bottom flask was added with NaBH₄ (0.228 g, 6.05 mmol). The reaction mixture was refluxed for 3 h, quenched with saturated NaHCO₃ solution and diluted with diethyl ether. The aqueous layer was further extracted with diethyl ether (3 x 50 mL) and the combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The product **18** was obtained in 98% yield. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.43-7.24 (m, 5H), 6.67-6.62 (d, 1H), 6.44-6.35 (m, 1H), 4.36-4.34 (d, 2H), 1.67 (s, 1H) ppm.

Preparation of (3R,4R)-4-(tert-butyldimethylsilyloxy)hexa-1,5-dien-3-ol (24)

tert-Butyldimethylsilyl chloride (TBSCl, 1.3205 g, 8.8 mmol) was added to a solution of C₂ symmetrical diene-diol (1.00 g, 8.80 mmol),^{21,22} imidazole (894.7 mg, 13.14 mmol), and dry dichloromethane (50 mL) in a sealable tube at 0 °C. The solution was allowed to room temperature for 16 h, quenched with water (30 mL), and diluted with ether (60 mL). The aqueous layer was further extracted with ether (20 mL x 3), and the combined organic layer was washed with aqueous HCl (0.1 N, 50 mL), saturated aqueous NaCl (50 mL), dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂, EtOAc/hexane-, 1:10; R_f 0.36) to give **24** (1.4719 g, 6.44 mmol, 74%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 5.87-5.74 (m, 2H), 5.33-5.15 (m, 4H), 3.97-3.90 (m, 2H), 2.56-2.55 (d, *J* = 4.56 Hz, 1H), 0.89 (s, 9H), 0.10-0.08 (d, *J* = 8.4 Hz, 6H) ppm.

Preparation of (4R,5R,E)-methyl 5-(tert-butyldimethylsilyloxy)-4-(methoxy)hepta-2,6-dienoate (26)

Chloromethyl methyl ether (MOMCl, 0.0106 mL, 0.1396 mmol) was added to a solution of **25** (20 mg, 0.0698 mmol), diisopropylethylamine (0.0365 mL, 0.2095 mmol), and dry dichloromethane (0.218 mL) in a sealed tube at 0 °C. The mixture was refluxed for 22 h, quenched with saturated NaHCO₃ solution, and extracted with dichloromethane (20 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by column chromatography (SiO₂) to give **26** (19.1 mg, 0.05779 mmol, 83%) as a light yellow oil. ¹H NMR (200 MHz, CDCl₃, 25 °C): δ = 6.93-6.82 (dd, 1H), 6.06-5.97 (dd, 1H), 5.87-5.71 (ddd, 1H), 5.28-5.12 (m, 2H), 4.74-4.60 (m, 2H), 4.25-4.08 (m, 2H), 3.71 (s, 3H), 3.35 (s, 3H), 0.88 (s, 9H), 0.03 (d, 6H) ppm.

Preparation of methyl 2-methylcyclopropanecarboxylate (15) (Table 1, entry 5)

To a suspension of sodium hydride (48 mg, 1.2 mmol) in dimethylformamide (0.5 mL) was added with trimethylsulfoxonium iodide (247.7 mg, 1.125 mmol). After all the hydrogen gas had been released (5 minutes), the mixture was stirred for another 15 minutes, and **14** (80

μL , 0.75 mmol) in dimethylformamide (1 mL) was added to the methylide. The mixture turned slightly yellow. Stirring was continued until 1 h. The mixture was poured into hydrochloric acid ice-water (20 mL, 3%), extracted with diethyl ether (3 x 20 mL), the ether extract was washed with saturated NaHCO_3 solution (20 mL) and water (4 x 20 mL). The combined ether layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was analyzed using ^1H NMR. The product formation was indicated by the emerging of new doublet peak about 1 ppm and two more peaks below 1 ppm.

Preparation of benzyl 2-methylcyclopropanecarboxylate (17) (Table 2, entry 5) via MIRC reaction

To a suspension of sodium hydride (48 mg, 1.2 mmol) in dimethylformamide (0.725 mL) was added with trimethylsulfoxonium iodide (247.7 mg, 1.125 mmol). After all the hydrogen gas had been released (5 minutes), the mixture was stirred for another 15 minutes, and **16** (132.1 mg, 0.75 mmol) in dimethylformamide (1 mL) was added to the methylide. The mixture turned slightly yellow. Stirring was continued until 4 h. The mixture was poured into hydrochloric acid ice-water (20 mL, 3%), extracted with diethyl ether (3 x 20 mL), the ether extract was washed with saturated NaHCO_3 solution (20 mL) and water (4 x 20 mL). The combined ether layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was analyzed using ^1H NMR. The product formation was indicated by the emerging of new doublet peak about 1 ppm and two more peaks below 1 ppm.

Preparation of benzyl 2-methylcyclopropanecarboxylate (17) (Table 2, entry 11) via Simmons-Smith reaction

To a sealed 10 mL round bottom flask containing 0.5 mL of freshly distilled dry diethyl ether was added with 1.26 mL (1.26 mmol) solution of 1 M diethyl zinc in *n*-hexane followed by addition of compound **16** (148 mg, 0.84 mmol) in 0.5 mL dry ether and diiodomethane (0.101 mL, 1.26 mmol) in 0 °C. The mixture was then refluxed for 8 h, quenched with saturated NaHCO_3 solution and diluted with diethyl ether. The aqueous layer was further extracted with diethyl ether (3 x 50 mL) and the combined organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was analyzed using ^1H NMR. The product formation was indicated by the emerging of new doublet peak about 1 ppm and two more peaks below 1 ppm.

Preparation of (2-phenylcyclopropyl)methanol (21) (Table 3, entry 3)

To a sealed 10 mL round bottom flask containing 1 mL of mixture dry dichloromethane and diethyl ether (1:4) was added with 1.5 mL (1.5 mmol) solution of 1 M diethyl zinc in *n*-hexane followed by addition of compound **18** (201.3 mg, 1.5 mmol) in 1.34 mL mixture solvent and diiodomethane (0.161 mL, 2 mmol) in 0 °C. The reaction was then increased to 30 °C for 17 h, quenched with saturated NaHCO_3 solution and diluted with diethyl ether. The aqueous layer was further extracted with diethyl ether (3 x 50 mL) and the combined organic layer was dried over Na_2SO_4 , filtered, and concentrated. The crude product was purified by column chromatography (SiO_2) to give **21** (152.4 mg, 1.028 mmol, 69%). ^1H NMR (300 MHz, CDCl_3 , 25 °C): δ = 7.26-7.03 (m, 5H), 3.60-3.48 (m, 2H), 1.82-1.77 (m, 1H), 1.75 (s, 1H), 1.57-1.37 (m, 1H), 0.99-0.89 (m, 2H) ppm.

Preparation of 2-phenylcyclopropanecarbaldehyde (22)

To a suspension of sodium hydride (48 mg, 1.2 mmol) in dimethylformamide (0.725 mL) was added with trimethylsulfoxonium iodide (247.7 mg, 1.125 mmol). After all the hydrogen gas had been released (5 minutes), the mixture was stirred for another 15 minutes, and **19** (99.1 mg, 0.75 mmol) in dimethylformamide (1 mL) was added to the methylide. The mixture turned slightly yellow. Stirring was continued until 4 h. The mixture was poured into hydrochloric acid ice-water (20 mL, 3%), extracted with diethyl ether (3 x 20 mL), the ether extract was washed with saturated NaHCO₃ solution (20 mL) and water (4 x 20 mL). The combined ether layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was analyzed using ¹H NMR.

Preparation of methyl 2-phenylcyclopropanecarboxylate (23)

To a suspension of sodium hydride (48 mg, 1.2 mmol) in dimethylformamide (0.725 mL) was added with trimethylsulfoxonium iodide (247.7 mg, 1.125 mmol). After all the hydrogen gas had been released (5 minutes), the mixture was stirred for another 15 minutes, and **20** (121.6 mg, 0.75 mmol) in dimethylformamide (1 mL) was added to the methylide. The mixture turned slightly yellow. Stirring was continued until 4 h. The mixture was poured into hydrochloric acid ice-water (20 mL, 3%), extracted with diethyl ether (3 x 20 mL), the ether extract was washed with saturated NaHCO₃ solution (20 mL) and water (4 x 20 mL). The combined ether layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was analyzed using ¹H NMR.

Preparation of methyl 2-((1*R*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-1-hydroxybut-3-enyl)cyclopropanecarboxylate (27)

To a sealed 10 mL round bottom flask containing **25** (80.0 mg, 0.2793 mmol) in 0.455 mL of the mixture dichloromethane and diethyl ether (1:4) was added with 0.279 mL (0.2793 mmol) solution of 1 M diethyl zinc in *n*-hexane followed diiodomethane (0.03 mL, 0.3724 mmol) in 0 °C. The mixture was then allowed to room temperature for 17 h, quenched with saturated NaHCO₃ solution and diluted with diethyl ether. The aqueous layer was further extracted with diethyl ether (3 x 50 mL) and the combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was analyzed using ¹H NMR.

Preparation of methyl 2-((5*R*,6*R*)-8,8,9,9-tetramethyl-6-vinyl-2,4,7-trioxa-8-siladecan-5-yl)cyclopropanecarboxylate (28) (Table 4, entry 2)

To a suspension of sodium hydride (10.8 mg, 0.2701 mmol) in tetrahydrofuran (0.8 mL) was added with trimethylsulfoxonium iodide (63.4 mg, 0.2881 mmol). After all the hydrogen gas had been released (5 minutes), the mixture was stirred for another 15 minutes, and **26** (59.5 mg, 0.18 mmol) in tetrahydrofuran (1 mL) was added to the methylide at 0 °C. The mixture turned slightly yellow. Stirring was continued until 5 h at 0 °C. The mixture was poured into hydrochloric acid ice-water (20 mL, 3%), extracted with diethyl ether (3 x 20 mL), the ether extract was washed with saturated NaHCO₃ solution (20 mL) and water (4 x 20 mL). The combined ether layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was analyzed using ¹H NMR.

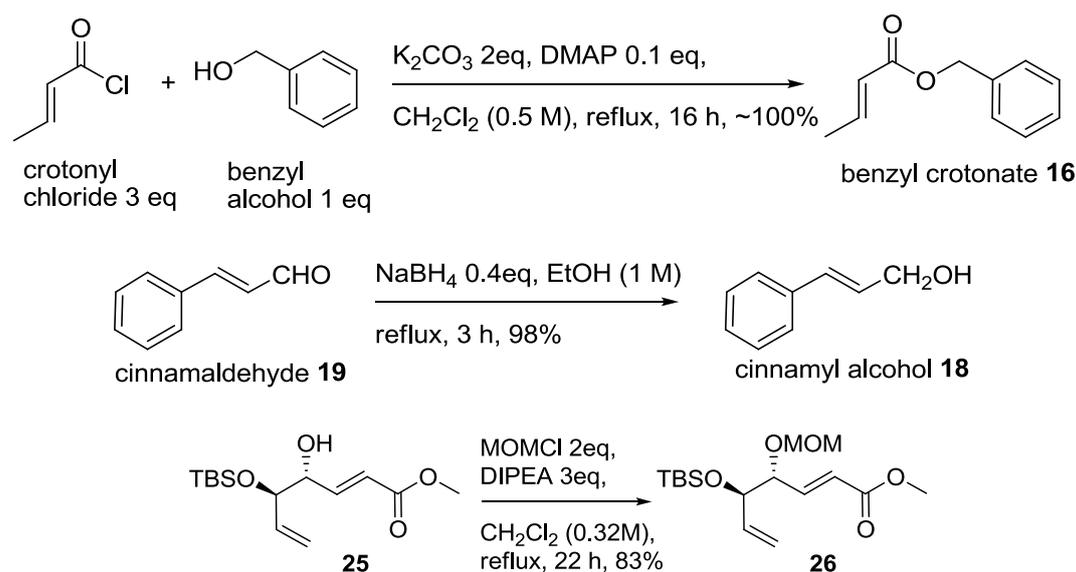


Figure 2. Preparation of compounds **16**, **18**, **25** and **26**

RESULT AND DISCUSSION

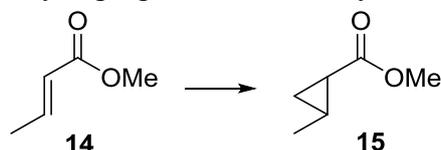
In the present work, we applied two different types of substrates for subjecting to the cyclopropanation, i.e., electron rich and electron deficient olefins, which are compatible to the nature of the electrophilic active species in the Simmons-Smith reagent (XZnCH_2Y) and nucleophilic sulfur ylide in the Michael-initiated ring closure reaction [12,13], respectively. These compounds were obtained either from commercial availability (compounds **14**, **19** and **20**), and by preparation (compounds **16**, **18**, **25**, and **26**). As shown in Figure 2, benzyl ester of crotonic acid **16** was successfully prepared by esterification of crotonyl chloride with benzyl alcohol in the presence of catalytic amount of 4-(dimethylamino)pyridine (DMAP). Cinnamyl alcohol **18** was simply provided by reduction of cinnamaldehyde using sodium borohydride. Compound **25** was prepared in our previous work by metathesis reaction between commercially available methyl acrylate and TBS-protected C_2 symmetrical diene which was derived from D-mannitol [19,20,21,22,25]. The subsequent protection as methoxymethyl ether gave compound **26** [23].

The cyclopropanation reaction using IZnCH_2I reagent, which was first used by Simmons and Smith proceeds stereospecifically through a “butterfly-type” transition state [14,15,16]. In this work, due to more practically applicable, the same class EtZnCH_2I reagent developed by Furukawa and co-workers prepared from ZnEt_2 and CH_2I_2 was used [17]. In the other hand, to cyclopropanate the substrates bearing electron withdrawing group, we adopted the idea applied by Ma’s Group using methylenedimethylsulfoxonium reagent [18]. The cyclopropanation of those various substrates was summarized in Table 1-4.

The cyclopropanation of methyl crotonate **14** was conducted through MIRC reaction since it bears an α,β -unsaturated carbonyl moiety, a typical Michael-acceptor in 1,4-addition reaction. As summarized in Table 1, performing the reaction either in dimethyl sulfoxide (DMSO) or in the mixture of DMSO with tetrahydrofuran (THF) was very sluggish (entry 1 to 4). It is rather surprising that none was observed in the NMR spectra of the crude reaction after work up. We suggested that due to the presence of trace of water in the very hygroscopic solvent, i.e. DMSO, the starting material was hydrolyzed into water-soluble crotonic acid and methanol under the reaction condition which were readily leached away during the work up

procedure. A slightly better opportunity was achieved when the reaction was performed in less hygroscopic dimethylformamide (DMF) (entry 5 to 6). Although achieved in quite low yield, the cyclopropane ring was formed as indicated from the NMR spectra of the crude reaction mixture. Further increase in reaction temperature significantly increased the degradation level of the starting material (entry 6).

Table 1. Cyclopropanation of methyl crotonate **14**



Entry	Reagent	Equivalent ^a	Solvent	Condition	Product (%) ^b
1	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMSO/THF 2.8:1 (0.195 M)	40 °C, 24 h	- ^c
2	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMSO/THF 1:2 (0.25 M)	40 °C, 4 h	- ^c
3	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMSO (0.264 M)	r.t., 3 h	- ^c
4	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMSO (0.264 M)	r.t., 2 h	- ^c
5	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.5 M)	r.t., 1 h	32.5
6	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.5 M)	r.t., 5 h	29.1
7	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.5 M)	40 °C, 1 h	47.0 ^c

^aThe starting material was set as 1; ^bcalculated from crude NMR; ^cthe crude mass was quite low

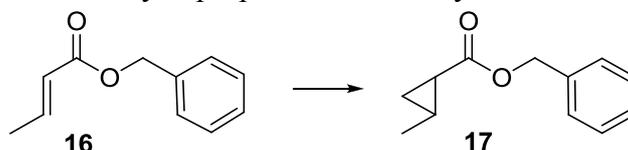
Our curiosity regarding to the possible degradation of starting material under the reaction condition led us to prepare the other substrate benzyl crotonate **16** which enabled us to detect the formation of undesired by-product. The cyclopropanation of compound **16** was summarized in Table 2. Again, performing the reaction in DMSO was not efficient due to the excellent dryness of this solvent is quite difficult to reach (entry 1). Valuable information was obtained from the NMR spectra of the crude reaction performed in dry DMF (entry 2 to 7). A huge proportion of benzyl alcohol clearly appeared in the crude NMR spectra indicating that hydrolysis of starting material during reaction condition did occur. This was also evidenced by the decreasing of the crude reaction mass to about a half compared to the corresponding starting material, which also happened with compound 14. Increasing the equivalence of the reagent could slightly increase the yield (entry 2 and 5). Further increase in the yield was observed by replacing NaH with KH (entry 7). The use of excess base (entry 4) was not favoured because it enhanced the hydrolysis of the starting material as well as the longer reaction time (entry 3). There was no significant difference of performing the reaction in low and room temperature under the reaction condition (entry 6).

The cyclopropanation of compound **16** using diethyl zinc and diiodomethane was also investigated. As shown in Table 2, the reaction was not proceed (entry 8 to 10) probably due to the incompatibility between the reagent and the substrate, i.e., the electrophilic nature of the active species EtZnCH₂I versus the electron deficient olefin of the substrate, even after the application of the more reactive reagent CF₃CO₂ZnCH₂I prepared by the addition of trifluoroacetic acid into the reaction mixture (entry 10) [12]. It is interesting to note that the reaction seemed to undergo in refluxing diethyl ether affording the product in 20.5% yield (entry 11).

The cyclopropanation of electron rich cinnamyl alcohol **18** was summarized in Table 3. The reaction performed without the additional solvent was not satisfied even in the presence of Lewis acid as a catalyst (entry 1) [24]. A moderate yield was achieved when the reaction was conducted in dry dichloromethane (entry 2) and increased significantly when the reaction

was allowed slightly longer in the mixture of dichloromethane and diethyl ether, even with less amount of diiodomethane (entry 3 and 4). The corresponding aldehyde **19** and ester **20** of this compound apparently did not suitable with the reaction condition (entry 5 and 6).

Table 2. Cyclopropanation of benzyl crotonate **16**

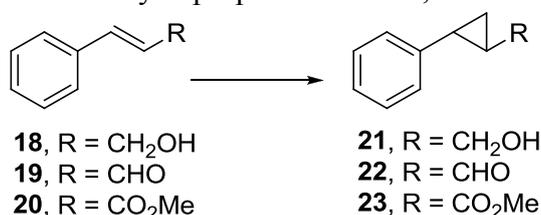


Entry	Reagent	Equivalent ^a	Solvent	Condition	Product (%) ^b
1	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMSO (0.264 M)	r.t., 2 h	- ^c
2	Me ₃ S(O)I, NaH	1.04, 1	dry DMF (0.435 M)	r.t., 4 h	55.3 ^{c,d}
3	Me ₃ S(O)I, NaH	1.04, 1	dry DMF (0.435 M)	r.t., 10 h	23.9 ^{c,d}
4	Me ₃ S(O)I, NaH	1.5, 2.5	dry DMF (0.435 M)	r.t., 4 h	- ^c
5	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.435 M)	r.t., 4 h	59.5 ^{c,d}
6	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.435 M)	0 °C, 4 h	59.8 ^{c,d}
7	Me ₃ S(O)I, KH	1.5, 1.6	dry DMF (0.435 M)	r.t., 4 h	64.3 ^{c,d}
8	Et ₂ Zn, CH ₂ I ₂	2, 2	dry CH ₂ Cl ₂ (0.05 M)	-12 – 30 °C, 24 h	SM
9	Et ₂ Zn, CH ₂ I ₂	2, 2	dry CH ₂ Cl ₂ (0.05 M)	-12 °C – r.t., 24 h	SM
10	Et ₂ Zn, CH ₂ I ₂ , TFA	2, 2, 2	dry CH ₂ Cl ₂ (0.05 M)	-78 °C – r.t., 24 h	SM
11	Et ₂ Zn, CH ₂ I ₂	2, 2	dry OEt ₂ (0.769 M)	reflux, 8 h	20.5

^athe starting material was set as 1; ^bcalculated from crude NMR; ^cthe benzyl part was detected in NMR of the crude reaction mixture; ^dthe crude mass was nearly a half of the mass of starting material.

Our effort to cyclopropanate an α,β -unsaturated ester bearing an allylic hydroxyl group, i.e. compounds **25** and **26**, was summarized in Table 4. However, compound **25** is apparently sufficient inactive toward the electrophilic EtZnCH₂I due to its electron withdrawing ester group (entry 1). In addition, as a typical Michael-acceptor, compound **26** also showed similar low reactivity with dimethylsulfoxonium methylide reagent (entry 2 to 4).

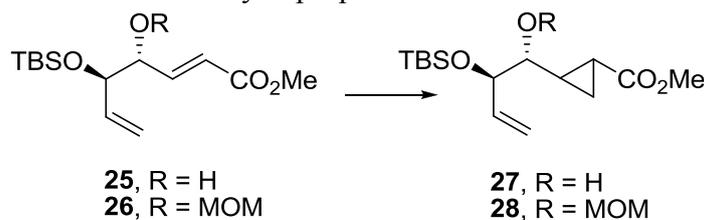
Table 3. Cyclopropanation of **18**, **19** and **20**



Entry	SM	Reagent	Equivalent ^a	Solvent	Condition	Product (%) ^b
1		Et ₂ Zn, CH ₂ I ₂ , TiCl ₄	1, 2, 0.05	<i>n</i> -hexane (1 M)	-78 – 0 °C, 2 h	42.7
2		Et ₂ Zn, CH ₂ I ₂	1, 2	dry CH ₂ Cl ₂ (0.1 M)	-12 °C – r.t., 12 h	77.6
3	18	Et ₂ Zn, CH ₂ I ₂	1, 1.33	dry CH ₂ Cl ₂ /OEt ₂ 1:4 (0.641 M)	0 – 30 °C, 17 h	69.0 ^c
4		Et ₂ Zn, CH ₂ I ₂	1, 1.33	dry CH ₂ Cl ₂ /OEt ₂ 1:4 (0.641 M)	0 °C – r.t., 20 h	~100
5	19	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.435 M)	r.t., 4 h	-
6	20	Me ₃ S(O)I, NaH	1.5, 1.6	dry DMF (0.435 M)	r.t., 4 h	SM

^athe starting material was set as 1; ^bcalculated from crude NMR; ^cisolated yield

Table 4. Cyclopropanation of **25** and **26**



Entry	SM	Reagent	Equivalent ^a	Solvent	Condition	Product (%) ^b
1	25	Et ₂ Zn, CH ₂ I ₂	1, 1.33	dry CH ₂ Cl ₂ /OEt ₂ 1:4 (0.641 M)	0 °C – r.t., 17 h	SM
2		Me ₃ S(O)I, NaH	1.5, 1.6	dry THF (0.1 M)	0 °C, 5 h	SM
3	26	Me ₃ S(O)I, NaH	2, 1.9	dry THF (0.5 M)	0 °C, 5 h	SM
4		Me ₃ S(O)I, NaH	1.5, 2	dry DMSO (0.3 M)	25 °C, 5 h	SM

^athe starting material was set as 1; ^bdetermined from the NMR spectra of crude reaction mixture

CONCLUSION

Cyclopropanation reaction of various substrates which could be divided into two different groups, electron rich and electron deficient olefins, has been performed using Simmons-Smith and MIRC reactions. Although it was very sensitive to the presence of water, the reaction of methyl crotonate 14 and benzyl crotonate 16 using methylenedimethylsulfonium underwent in dry DMF in smooth condition. Cinnamyl alcohol 18 acted as a good substrate for the Simmons-Smith cyclopropanation allowing it to excellent reaction yield. In the other hand, compounds 19, 20, 25, and 26 were apparently not suitable to the reaction condition set in our study.

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