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Applications of 1-Alkenyl-1,1-Heterobimetallics in the Stereoselective Synthesis of Cyclopropylboronate Esters, Trisubstituted Cyclopropanols and 2,3-Disubstituted Cyclobutanones

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Abstract

1-Alkenyl-1,1-heterobimetallics are potentially very useful in stereoselective organic synthesis, but are relatively unexplored. Introduced herein is a practical application of 1-alkenyl-1,1-heterobimetallic intermediates in the synthesis of versatile cyclopropyl alcohol boronate esters, which are valuable building blocks. Thus, hydroboration of 1-alkynyl-1-boronate esters with dicyclohexylborane generates 1-alkenyl-1,1-diboro species. In situ transmetalation with dialkylzinc reagents furnishes 1-alkenyl-1,1-borozinc heterobimetallic intermediates. Addition of the more reactive Zn–C bond to aldehydes generates the key B(pin) substituted allylic alkoxide intermediates. An in situ alkoxide directed cyclopropanation proceeds with the formation of two more C–C bonds, affording cyclopropyl alcohol boronate esters with three new stereocenters in 58–89% isolated yields and excellent diastereoselectivities (>15:1 dr). Oxidation of the B–C bond provides trisubstituted α-hydroxycyclopropyl carbinols as single diastereomers in excellent yields (75–93%). Facile pinacol-type rearrangement of the α-hydroxycyclopropyl carbinols provides access to both *cis*- and *trans*-2,3-disubstituted cyclobutanones with high stereoselectivity (>17:1 dr in most cases) from a common starting material. This methodology has been applied in the synthesis of quercus lactones A and B.

1. Introduction

The development of new methods for the stereoselective construction of C–C bonds remains a fundamental and important goal in organic synthesis.[1–3] With modern synthetic design demanding high efficiency, an appealing strategy is the advancement of novel tandem reactions whereby sequential transformations can be performed without isolation or purification of intermediates.[4–10] Such a strategy minimizes the number of synthetic steps while maximizing the molecular complexity and yield.

One approach to efficiently introduce molecular complexity entails generation of functionalized 1,1-heterobimetallic intermediates, wherein each metal-carbon bond exhibits distinct reactivity that can be selectively exploited in C–C bond-forming reactions or functional group manipulations.[11–13] Despite the potential usefulness of these reagents, 1,1-bimetallics are rarely applied to synthesis, most likely because of their high reactivity and difficult preparation and handling. The vast majority of investigations of 1,1-bimetallic reagents involve

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sp^3 hybridized bimetallics.[11, 13–16] In contrast, 1-alkenyl-1,1-bimetallics have received considerably less attention, largely due to difficulties controlling double bond geometry,[12, 13] multistep preparations, or limited functional group tolerance.[17, 18] The challenges in generation and reactions of 1-alkenyl-1,1-bimetallics are highlighted in Scheme 1.

Early work by Knochel and coworkers explored the chemistry of 1-alkenyl-1,1-heterobimetallics wherein bimetallics of boron and zinc or copper were generated to synthesize α-hydroxy ketones.[17] Further development and applications of these reagents were thwarted by loss of double bond stereochemistry during the formation of the bimetallic reagent. Srebnik and coworkers successfully addressed this limitation by generation of bimetallics of boron and zirconium via hydrozirconation of B(pin) alkynes with Schwartz's reagent (Cp_2ZrHCl). Transmetalation from zirconium to zinc was followed by a Negishi coupling to give B(pin) substituted dienes.[19–21] Use of stoichiometric Schwartz's reagent remains prohibitively expensive (> $2,000/mole) at this time. Soderquist and coworkers generated 1-alkenyl-1,1-diboro intermediates by hydroboration of alkynylborinates with dicyclohexylborane, which were selectively protodeborylated with acetic acid to form (*Z*)-vinyl boranes.[22]

To address the challenges in the synthesis and applications of 1-alkenyl-1,1-bimetallics, we recently reported a practical generation of 1,1-heterobimetallics from air-stable B(pin)-substituted alkynylboronate esters and demonstrated their utility in a variety of one-pot transformations to provide boronate substituted allylic alcohols, dienols, α-hydroxy ketones, and protected α,β-dihydroxy ketones with high diastereoselectivity (Scheme 2).[23] Thus, hydroboration of air stable alkynyldioxaborolane with dicyclohexylborane proceeded regioselectively to cleanly generate the new 1,1-diboro intermediates, as judged by ^{1}H, ^{11}B{^{1}H}, and ^{13}C{^{1}H} NMR spectroscopy. Our 1,1-diboro bimetallic intermediates were recently employed in the stereoselective synthesis of (*Z*)-alkenyl pinacolboronates by Molander.[24] The key to success of the tandem reactions in Scheme 2 is the selective transmetalation of the Cy_2B–vinyl bond with dialkylzinc reagents to generate the 1,1-bimetallic intermediates of zinc and B(pin).[25] The difference in reactivity between vinylzinc and vinylboronate esters is enormous, as demonstrated by the selective reaction of the 1,1-heterobimetallic intermediates with aldehydes at the Zn–C bond to generate functionalized boronate esters with complete control over the double bond geometry (Scheme 2). The allylic alcohol product is the net *trans* hydroboration of a propargylic alcohol. Of course, *trans* hydroboration is extremely rare.[26]

Herein we disclose an efficient and highly diastereoselective tandem route to the synthesis of substituted cyclopropanes based on our 1,1-heterobimetallic chemistry. Numerous natural and unnatural products containing cyclopropyl groups exhibit important biological activity.[27–29] These strained cycloalkanes are also valuable intermediates in organic synthesis, allowing access to either functionalized cyclopropanes or ring-opened products.[30] As a result, their synthesis has received much attention.[31,32] An efficient route to stereodefined cyclopropyl boronate esters and their oxidation to trisubstituted α-hydroxycyclopropyl carbinols is outlined below. We also document their facile acid-catalyzed pinacol-type rearrangement to either *cis*- or *trans*-2,3-disubstituted cyclobutanones with high stereoselectivity from a common starting material. This methodology has been applied to the synthesis of quercus lactones A and B from a common precursor.

2. Experimental Section

General Methods

All reactions were performed under a nitrogen atmosphere with oven-dried glassware. All manipulations involving dicyclohexylborane, dimethylzinc and diethylzinc were carried out under an inert atmosphere in a Vacuum Atmospheres drybox with an attached MO-40 Dritrain

or using standard Schlenk or vacuum line techniques. Chemicals were obtained from Aldrich, Acros, or GFS Chemicals unless otherwise specified. Solvents were purchased from Fischer Scientific. Toluene, dichloromethane, diethyl ether and hexanes were dried through activated alumina columns. Tetrahydrofuran was distilled from sodium and benzophenone. HPLC grade chloroform was used. Liquid substrates were distilled prior to use. B(pin) substituted alkynes were prepared by literature methods.[33–38] Dimethylzinc and diethylzinc (1.0 M or 2.0 M in toluene) was prepared and stored in a Vacuum Atmospheres drybox. NMR spectra were obtained on a Brüker 300, 360, 400 or 500 MHz Fourier transform spectrometer at the University of Pennsylvania NMR facility. ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent. $^{11}B\{^{1}H\}$ NMR spectra were referenced to $BF_3{\cdot}OEt_2$. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. HRMS data was obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using electrospray ionization in positive or negative mode, depending on analyte. Melting points were determined on a Uni-melt Thomas Hoover melting point apparatus and are uncorrected. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light or by staining with cerric ammonium molybdate or phosphomolybdic acid solutions. Silica gel (Silicaflash, P60, 40–63 μm, Silicycle) was used for air-flashed chromatography, and deactivated silica gel was prepared by addition of 15 mL of Et_3N to 1 L of silical gel. Complete experimental procedures and characterization are located in the Supporting Information.

Caution—Dialkylzinc reagents are pyrophoric. Care must be used when handling them.

General Procedure A: Synthesis of Cyclopropyl Boronate Esters

To a suspension of $HBCy_2$ (107 mg, 0.60 mmol) in toluene (1.0 mL) under N_2 was added alkyne-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (0.60 mmol) and the reaction mixture was stirred for 30 min at rt, after which it was homogeneous. The reaction vessel was cooled to −78 °C and treated with Me_2Zn (0.30 mL, 2.0 M in toluene, 0.60 mmol) for 30 min. The solution was then warmed to −10 °C, and the aldehyde (0.40 mmol) was added. The reaction mixture was stirred at −10 °C until TLC showed complete consumption of the aldehyde. The volatile materials were removed under reduced pressure and Et_2Zn (1.0 mL, 2.0 M in toluene, 2.0 mmol), CF_3CH_2OH (0.15 mL, 2.0 mmol), and CH_2I_2 (0.16 mL, 2.0 mmol) were sequentially added at 0 °C. The reaction vessel was wrapped in aluminium foil to exclude light and allowed to stir at rt for 24 h. The reaction mixture was then diluted with EtOAc (4 mL) and quenched with saturated NH_4Cl (4 mL) at 0 °C. The organic layer was separated and the aqueous solution was extracted with EtOAc (3 × 20 mL). The combined organic solution was dried over $MgSO_4$, filtered through celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

[2-Butyl-1-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-cyclopropyl]-cyclohexyl-methanol (Table 2, entry 7)

The product was prepared by General Procedure A using cyclohexanecarbaldehyde (44.9 mg, 0.40 mmol) and 2-hex-1-ynyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane (125.9 mg, 0.60 mmol). The crude product was purified by flash column chromatograghy on silica gel (hexanes:EtOAc = 96:4) to afford an oil (115.7 mg, 86%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.49 – 0.50 (m, 1H), 0.64 – 0.66 (m, 1H), 0.74 – 0.78 (m, 1H), 0.86 – 0.96 (m, 5H), 1.09 – 1.17 (m, 1H), 1.19 (s, 12H), 1.28 – 1.41 (m, 6H), 1.52 – 1.56 (m, 1H), 1.61 – 1.68 (m, 2H), 1.71 – 1.80 (m, 4H), 2.01 – 2.04 (m, 1H), 2.11 (br, 1H), 2.29 (br, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz) δ 14.3, 17.6, 22.8, 24.8, 24.9, 26.5, 26.80, 26.82, 30.1, 30.4, 32.3, 44.8, 83.0, 85.4; $^{11}B\{^{1}H\}$ NMR ($CDCl_3$, 128 MHz) δ 31.4; IR (neat) 3461, 2930, 1420, 1147 cm^{-1}; HRMS *m/z* 318.2679 $[(M–H_2O)^{+}$; calcd for $C_{20}H_{35}BO_2$: 318.2671].

General Procedure B: Synthesis of α-Hydroxycyclopropyl Carbinols

To a solution of cyclopropanol boronate ester (2.0 mmol) in a 1:1 mixture of THF:H_2O (20 mL each) was added $NaBO_3{\cdot}H_2O$ (599 mg, 6.0 mmol) at rt. The reaction suspension was stirred at rt for 2–6 h until the reaction was complete by TLC. Water was added (20 mL), and the solution was extracted with Et_2O (3 × 30 mL). The combined diethyl ether phase was washed with brine, dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel to obtain the pure α-hydroxycyclopropyl carbinols as white crystalline solids.

2-Butyl-1-(hydroxy(cyclohexyl)methyl)cyclopropanol (Table 3, entry 1)

The product was prepared by General Procedure B using [2-butyl-1-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-cyclopropyl]-cyclohexyl-methanol (149 mg, 0.44 mmol), $NaBO_3\delta H_2O$ (133 mg, 1.33 mmol) in THF/H_2O (6 mL: 6 mL). The crude product was purified by flash column chromatography on silica gel (hexanes:EtOAc = 80:20) to obtain the cyclopropanol as a white crystalline solid (89 mg, 89% yield). MP 91 – 93 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.25 (t, *J* = 5.7 Hz, 1H), 0.59 (dd, *J* = 5.1, 9.5 Hz, 1H), 0.72 – 0.80 (m, 1H), 0.84 – 1.00 (m, 5H), 1.07 – 1.44 (m, 8H), 1.56 – 1.85 (m, 6H), 2.05 (d, *J* = 12.4 Hz, 1H), 2.33 (br, 1H), 2.56 (d, *J* = 8.9 Hz, 1H), 2.68 (b, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 14.3, 17.0, 22.9, 24.2, 26.2, 26.3, 26.7, 26.9, 29.5, 30.2, 32.0, 41.0, 60.6, 83.5; IR (neat) 3300, 2919, 2846, 1449, 1240 cm^{-1}; HRMS *m/z* 209.1914 [(M-OH)$^+$; calcd for $C_{14}H_{25}O$: 209.1905]. The product was crystallized from MeOH/H_2O and single crystal X-ray structure has been obtained. See Supporting Information Part 2.

General Procedure C: Synthesis of *cis*-2,3-Disubstituted Cyclobutanones

To a solution of the α-hydroxycyclopropyl carbinol (0.34 mmol) in $CHCl_3$ (5 mL) was added a catalytic amount of *p*-TsOH·H_2O (6.5 mg, 0.034 mmol) at rt. The reaction mixture was stirred at rt until the reaction was complete by TLC (20 min to 2 h). The reaction mixture was then quenched with saturated $NaHCO_3$ (3 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined diethyl ether phase was washed with brine, dried with anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford the *cis*-2,3-disubstituted cyclobutanone as an oil. In most cases, the crude product was pure by ^{1}H NMR (purity >95%), and further purification by flash column chromatography was usually avoided. This procedure consistently gave better yields than General Procedure D.

General Procedure D: Synthesis of *cis*-2,3-Disubstituted Cyclobutanones

To a solution of the α-hydroxycyclopropyl carbinol (0.16 mmol) in dry THF (4 mL) was added a catalytic amount of $BF_3{\cdot}OEt_2$ (4 μL, 4.5 mg, 0.032 mmol) at rt. The reaction mixture was stirred at rt until the reaction was complete by TLC (2–6 h). The reaction mixture was then hydrolyzed with H_2O (3 mL). The solution was extracted with CH_2Cl_2 (3 × 4 mL), washed with brine, dried with anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on deactivated silica gel (pentane/diethyl ether) to afford the *cis*-2,3-disubstituted cyclobutanone as an oil.

General Procedure E: Synthesis of *trans*-2,3-Disubstituted Cyclobutanones with *p*-TsOH·H_2O at rt

To a solution of the α-hydroxycyclopropyl carbinol (0.14 mmol) in $CHCl_3$ (3 mL) was added a catalytic amount of *p*-TsOH·H_2O (5.1 mg, 0.027 mmol) at rt. The reaction was stirred at rt for 12 h, after which the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (pentane/diethyl ether) to afford the

trans-2,3-disubstituted cyclobutanone as an oil. Yields are usually higher with this procedure than General Procedure F.

General Procedure F: Synthesis of *trans*-2,3-Disubstituted Cyclobutanones with *p*-TsOH·H_2O at Reflux

To a solution of the α-hydroxycyclopropyl carbinol (0.14 mmol) in $CHCl_3$ (3 mL) was added a catalytic amount of *p*-TsOH·H_2O (5.1 mg, 0.027 mmol) at rt. The reaction was refluxed for 1 h, and then let it cool to rt, after which the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (pentane/diethyl ether) to afford the *trans*-2,3-disubstituted cyclobutanone as an oil.

cis-3-Butyl-2-cyclohexylcyclobutanone (Table 4, entry 1)

The product was prepared by General Procedure C using 2-butyl-1-(hydroxy(cyclohexyl) methyl)cyclopropanol (51.8 mg, 0.23 mmol) and *p*-TsOH·H_2O (4.4 mg, 0.023 mmol) in $CHCl_3$ (3 mL) to obtain the cyclobutanone as an oil (44.6 mg, 94% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3H), 0.96 – 1.07 (m, 1H), 1.08 – 1.45 (m, 9H), 1.54 – 1.81 (m, 6H), 2.16 (d, *J* = 13.2 Hz, 1H), 2.28 – 2.47 (m, 2H), 2.92 – 3.10 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 14.3, 22.9, 26.0 (two overlapping carbons), 26.6, 27.5, 29.8, 30.4, 31.6, 32.8, 35.0, 49.8, 67.8, 211.0; IR (neat) 2925, 2853, 1776, 1450 cm^{-1}; HRMS *m/z* 209.1898 [$(MH)^+$; calcd for $C_{14}H_{25}O$: 209.1905].

trans-3-Butyl-2-cyclohexylcyclobutanone (Table 4, entry 1)

The product was prepared by General Procedure E using 2-butyl-1-(hydroxy(cyclohexyl) methyl)cyclopropanol (37.1 mg, 0.16 mmol) and *p*-TsOH·H_2O (6.2 mg, 0.032 mmol) in $CHCl_3$ (3 mL) to obtain the cyclobutanone as an oil (30.0 mg, 90% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.0 Hz, 3H), 0.94 – 1.07 (m, 2H), 1.08 – 1.39 (m, 7H), 1.41 – 1.51 (m, 1H), 1.52 – 1.77 (m, 6H), 1.90 (d, *J* = 13.4 Hz, 1H), 2.03 – 2.14 (m, 1H), 2.49 (ddd, *J* = 3.5, 6.9, 17.5 Hz, 1H), 2.57 – 2.65 (m, 1H), 2.93 (ddd, *J* = 2.8, 8.9, 17.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 14.2, 22.8, 26.1, 26.3, 26.5, 29.0, 30.7, 30.8, 31.4, 36.8, 38.6, 49.9, 71.6, 211.7; IR (neat) 2925, 2853, 1775, 1450 cm^{-1}; HRMS *m/z* 190.1722 [$(M–H_2O)^+$; calcd for $C_{14}H_{22}$: 190.1722].

3. Results and Discussion

3.1. Stereoselective Synthesis of Cyclopropyl Boronate Esters

The importance of selectively functionalized cyclopropane moieties in natural product and medicinal chemistry, and their utility in synthesis, inspired us to develop an efficient route to substituted cyclopropanes beginning with 1,1-bimetallic intermediates. Thus, regioselective hydroboration of alkynyldioxaborolane followed by chemoselective transmetalation affords the 1,1-borozinc bimetallic, which adds to aldehydes to generate allylic alkoxides (Scheme 3).[23] We envisaged an in situ alkoxide directed cyclopropanation would afford the cyclopropyl boronate esters. Performing these reactions in tandem would result in formation of three C–C bonds and stereocenters.

3.1.1. Optimization of Tandem Carbonyl Addition/Cyclopropanation Reactions

—The Simmons-Smith cyclopropanation is a well established method for cyclopropane synthesis[39, 40] that has been further developed since its introduction.[31, 41] Perhaps the most significant improvement is the Furukawa modification, which allows generation of the carbenoid by alkyl exchange between Et_2Zn and CH_2I_2 to form the active species $EtZnCH_2I$ or $Zn(CH_2I)_2$.[42–44] Wittig[45–48] and Denmark's[49, 50] halomethylzinc reagents, $(XCH_2)_2Zn$ (X = Cl, Br) and $ClZnCH_2I$, and Shi's tunable zinc reagents (Y– Zn–CH_2I, Y = $EtO^–$,

$CF_3CH_2O^-$, $CF_3CO_2^-$, $PhCO_2^-$ etc.) are also notable modifications.[51–53] The generated B(pin) substituted allylic alkoxide intermediate in Scheme 3 was treated with these cyclopropanation reagents to optimize diastereoselectivity and yields (Table 1). $EtZnCH_2I$[42–44, 54, 55] was prepared from Et_2Zn (5 equiv) and CH_2I_2 (5 equiv) and gave 40% conversion of the allylic alkoxide to the cyclopropane after 2 d at rt (entry 1). $IZnCH_2I$ was not an effective reagent in this transformation, giving less than 10% conversion (entry 2). Conversions as high as 95% were obtained with $Zn(CH_2I)_2$,[45, 47] generated from Et_2Zn (5 equiv) and CH_2I_2 (10 equiv). The separation of the desired cyclopropanes from trace amounts of B(pin) allylic alcohol product (5%) was difficult and thus complete conversion of the allylic alkoxide to the cyclopropyl alcohol was required. The cyclopropanation reached completion when conducted at 40 °C with $Zn(CH_2I)_2$ (entry 4), however some isomerization of the vinyl boronate esters was observed. We hypothesized that the dicyclohexylmethylborane byproduct, formed in the transmetalation step, reacted with the cyclopropanation reagent. Therefore, after formation of the allylic alkoxide, all volatile materials were removed under reduced pressure, followed by addition of cyclopropanation reagents to the reaction mixture. In entries 5 and 6, Shi's zinc reagents[51–53] $CF_3COOZnCH_2I$ and $CF_3CH_2OZnCH_2I$ failed to achieve full conversion to the cyclopropanes. To increase the likelihood of complete conversion, we conducted the cyclopropanation at higher concentrations. We were pleased to observe complete reaction under more concentrated conditions. Thus after removal of the volatile materials, Et_2Zn (2 M in toluene) and neat CF_3CH_2OH and CH_2I_2 (5 equiv each) were added to form the carbenoid $CF_3CH_2OZnCH_2I$. Noteworthy is the difference between using 1 M Et_2Zn (entry 6) and 2 M Et_2Zn (entry 7) in the cyclopropanation step, highlighting the importance of the concentration of active zinc reagents.

3.1.2. Substrate Scope of the Carbonyl Addition/Cyclopropanation Reactions—

Employing the optimized conditions in Table 1 (entry 7), a series of aromatic and aliphatic aldehydes were investigated in the tandem addition/cyclopropanation reactions. As shown in Table 2, benzaldehyde and its derivatives with substitution at *meta*- or *para*- position (entries 1–6) underwent the addition/cyclopropanation in 58–89% isolated yield and excellent diastereoselectivities (>20:1 in all cases). Likewise, aliphatic aldehydes gave the corresponding cyclopropylboronate esters in 58–86% isolated yield and excellent diastereoselectivities (>15:1, entries 7–10). The dr's in Table 2 were determined by ^1H NMR of the crude reaction products. The relative stereochemistry was determined by X-ray crystallography after derivatization, as outlined in subsequent sections. Under the conditions outlined in Table 1, ketones do not undergo reaction with 1,1-bimetallic reagents.

The scalability of this method was demonstrated in the synthesis of cyclopropylboronate ester in entry 1 on a 5 and 10 mmol scale, affording 1.7 g (79% yield) and 2.5 g (75% yield), respectively. It is generally accepted that Simmons-Smith cyclopropanations proceed via a "butterfly-type" transition state.[41, 56] On the basis of this model, a possible transition state for the cyclopropanation is shown in Figure 1.

3.2. Stereoselective Synthesis of α-Hydroxycyclopropyl carbinols

Substituted cyclopropanols exhibit diverse reactivity and are valuable synthetic intermediates.[57–60] For instance, they formally act as homoenolates via ring cleavage reactions and readily undergo ring expansion.[57] Recognizing the importance of cyclopropyl alcohols, Cha set out to prepare trisubstituted cyclopropanols using the titanium-mediated Kulinkovich cyclopropanation[61, 62] of chiral α-alkoxy aldehydes with *n*-BuMgBr.[63] The cyclopropane products were isolated as an inseparable mixture of the four possible diastereomers (1.0:0.7:0.3:0.25) in 57% yield (Scheme 4, A). Kulinkovich made similar observations upon treating isopropyl α-isopropoxyvalerate with *i*-PrMgBr and titanium tetraisopropoxide.[64] The

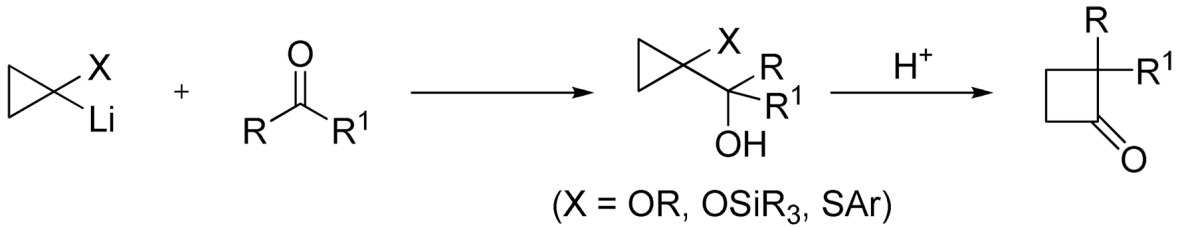
corresponding cyclopropanols were obtained as a mixture of all four possible diastereomers in approximately equal amounts (Scheme 4, B).[64]

With the goal of accessing cyclopropanols from our cyclopropyl boronate esters, we examined several reagents to oxidize the B–C bond. Traditional $NaOH/H_2O_2$ oxidation gave poor yields of the cyclopropanol along with ring cleaved carbonyl compounds.[65–67] Oxidation of the B–C bond with sodium perborate[68] in a 1:1 THF:H_2O mixture fortunately provided the desired trisubstituted cyclopropane diols as single diastereomers in excellent yields (Table 3). As shown, a variety of aliphatic (entries 1–3) and aromatic (entries 4–8) cyclopropyl boronate esters were smoothly oxidized to the corresponding α-hydroxy cyclopropyl carbinols in 75–93% isolated yield. In all instances, only one diastereomer was detected by ^{1}H NMR spectroscopy. X-ray crystal structures of entries 1, 2 and 7 in Table 3 (see Supporting Information for details) revealed that the cyclopropyl moiety is *syn* to the secondary hydroxyl group, confirming that the oxygen insertion into the B–C bond proceeded with retention.[69, 70]

3.3. Diastereoselective Synthesis of 2,3-Disubstituted Cyclobutanones

Cyclobutanones are useful synthetic intermediates and are found in bioactive natural and unnatural products.[71–73] The most common method to synthesize cyclobutanones is via [2 + 2] cycloadditions of ketenes with alkenes. This approach works well with highly nucleophilic ketenophiles such as conjugated dienes and enol ethers. Unactivated alkenes are poor substrates for ketene and alkyl- or aryl-substituted ketenes.[74] Furthermore, this approach to cyclobutanones is complicated by competitive dimerization of ketene.[75] These problems are usually circumvented by employing dichloroketene.[76] Although the increased reactivity of dichloroketene is advantageous, additional steps are required to reduce the undesired chlorides. In addition, Stryker synthesized *trans*-2,3-disubstituted cyclobutanones by a novel carbonylation of titanacyclobutane complexes.[77] This method has yet to be applied to the more challenging *cis*-isomers.[77] A clever approach to enantioenriched *trans*-2,3-disubstituted cyclobutanones involves desymmetrization of 3-aryl cyclobutanones via an asymmetric deprotonation/alkylation sequence.[78] This cyclobutanone functionalization works best with primary alkyl halides, which are good substrates for this S_N2 substitution. The *cis*-isomers cannot be prepared by this approach.

A different approach to prepare cyclobutanones involves generation of heteroatom-substituted cyclopropyl carbinols from aldehydes and ketones and subsequent ring expansion. The heteroatom facilitates the rearrangement to afford the cyclobutanone after hydrolysis (eq 1).[79–83] The acid or heat induced ring expansion of oxaspiro[2,2]pentanes provides another route to cyclobutanones (eq 2).[84–90] Similar pinacol-type rearrangements, promoted by Brønsted acids, Lewis acids and bases have also been reported for α-hydroxycyclopropyl carbinols (eq 3).[63, 91–95] Use of this approach for the diastereoselective synthesis of both *cis*- and *trans*-2,3-disubstituted cyclobutanones has been problematic, partly due to difficulties in the preparation of highly diastereoenriched trisubstituted α-hydroxycyclopropyl carbinols.[63, 64]



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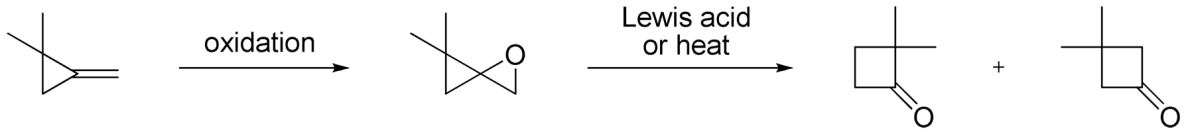
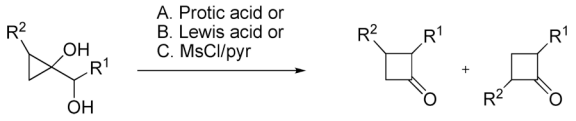


(2)



(3)

To address the challenges in the synthesis of *cis*- and *trans*-2,3-disubstituted cyclobutanones, we treated the cyclopropane diol in Scheme 5 with sulfonyl chlorides in pyridine and with a series of Lewis and Brønsted acids. MsCl and mesitylenesulfonylchloride in pyridine gave a 7:1 and 10:1 dr, respectively, both favoring the *trans* diastereomer. When catalytic *p*-TsOH (10 mol %) was employed, *trans*-2,3-disubstituted cyclobutanone was obtained with a 17:1 dr in 94% yield. In sharp contrast, use of $BF_3{\cdot}OEt_2$ furnished the *cis* diastereomer in 17:1 dr and 80% yield. Thus, both the *cis*- and *trans*-2,3-disubstituted cyclobutanones are accessible with excellent diastereoselectivity and high yields from a single precursor. In addition, when cyclohexyl was used in place of the phenyl group in Scheme 5, either the *cis* or *trans* diastereomers could be obtained with >20:1 dr using $BF_3{\cdot}OEt_2$ or 10 mol % *p*-TsOH, respectively.

The predominant formation of the *cis* isomer can be rationalized by a concerted rearrangement of conformer A (Figure 2) where ring expansion proceeds via an antiperiplanar transition state with breakage of bond *a*. In ring expansion via conformer B the least substituted C–C bond (*b*) would migrate, which is less favorable (Figure 2) as migration of the more substituted carbon of the cyclopropyl ring is well documented.[96–99] While the *cis*-isomer can be explained by a concerted pinacol-type rearrangement of the cyclopropane diol (Figure 2), two possible reaction pathways could explain the formation of the *trans*-diastereomer. The first involves a double inversion and proceeds via an oxaspiropentane (eq 2). Fukumoto demonstrated that oxaspiropentanes, formed by epoxidation of alkylidene cyclopropanes,[100, 101] readily rearrange to cyclobutanones.[89, 90] The second possibility involves isomerization of the kinetic *cis* product to the thermodynamic *trans* product via enol formation. Treatment of the cyclopropane diol in Figure 2 with catalytic *p*-TsOH at rt followed by quenching after 30 min with saturated $NaHCO_3$ at 0 °C resulted in cyclobutanone with a *cis*: *trans* ratio of >20:1. Prolonged treatment with *p*-TsOH, however, furnished the *trans*-isomer with 1:17 dr. This result indicates that the *cis*-product can be equilibrated to the *trans*.

With these optimized conditions, a series of alkyl and aryl α-hydroxycyclopropyl carbinols were shown to smoothly rearrange to *cis*- or *trans*-2,3-disubstituted cyclobutanones with excellent yields and diastereoselectivity (Table 4). Method A–i cleanly led to *cis* isomers in 94–99% isolated yield and >17:1 dr. No purification was required in these cases. Although they can also be obtained with $BF_3{\cdot}OEt_2$ in THF in 1–2 h (Method A-ii), this method provided lower yields. Nevertheless, the advantage of the latter method is that the *cis* isomer did not isomerize under our reaction conditions, even with prolonged reaction times. On the other hand, the *trans* isomer can be obtained either by refluxing the *cis* isomer in $CHCl_3$ for 1–2 h or by allowing the reaction to proceed for 12–24 h at rt in a minimal amount of solvent (77–

90% yield). Entry 3 readily formed the *cis* isomer, but could only be isomerized to the *trans* isomer with 5:1 dr, probably due to the smaller size of the Me group relative to substituents in other substrates (Table 4). We are unaware of other routes that allow access to *both* the *cis*- and *trans*-diastereomers of 2,3-disubstituted cyclobutanones with excellent dr.

3.4. Diastereoselective Synthesis of (±)-Quercus Lactones A and B

Many natural products and intermediates contain γ-butyrolactones,[102] which are accessible through Baeyer-Villiger oxidation of cyclobutanones. Examples of such lactones are the quercus lactones A and B and the quagnac lactones A and B.[103] These compounds have been isolated from white oak wood and are found in wines and spirits stored in oak barrels for maturing.[103] To demonstrate the utility of our methods, we performed a short diastereoselective synthesis of quercus lactones A and B. Thus, hydroboration of the methylalkynyldioxaborolane[37,38] with dicyclohexylborane followed by in situ transmetalation with dimethyl zinc provided the 1,1-bimetallic intermediate (Figure 3). Subsequent addition to *n*-pentanal followed by in situ cyclopropanation generated the α-hydroxycyclopropyl boronate ester (86% yield). Oxidation with $NaBO_3 \cdot H_2O$ generated the a-hydroxycyclopropyl carbinol (91% yield), which underwent facile pinacol rearrangement to afford the corresponding *cis*-cyclobutanone. The *trans*-cyclobutanone was prepared by rearrangement/isomerization. As previously described, *cis*-cyclobutanone precursor of quercus lactone B could be obtained in >20:1 dr (Table 4, entry 3A). The intermediate for quercus lactone A, however, was generated as a 5:1 mixture of diastereomers (Table 4, entry 3B). Subsequent Baeyer-Villiger oxidation ultimately furnished quercus lactone B with >20:1 dr and quercus lactone A with a 5:1 dr, as determined by ^{1}H NMR spectroscopy.

4. Summary and Outlook

In this report, we demonstrate the utility of 1,1-heterobimetallic reagents in the synthesis of cyclopropane boronate esters α-hydroxycyclopropyl carbinols, and *cis* and *trans*-2,3-disubstituted cyclobutanones with excellent diastereoselectivities. Generation of 1-alkenyl-1,1-heterobimetallic species based on hydroboration with dicyclohexylborane of readily available and air stable B(pin) substituted alkynes.[23] The B-vinyl bond of the dicyclohexyl alkenyl borane undergoes rapid and chemoselective transmetalation with dialkylzinc reagents to generate 1,1-heterobimetallic complexes. These boron/zinc heterobimetallic reagents are mild, functional group tolerant and readily undergo addition of the more reactive Zn–C bonds to aldehydes to generate the key B(pin) substituted allylic alkoxide intermediates.[23] Herein we developed an in situ alkoxide directed cyclopropanation to afford cyclopropyl boronate esters in good isolated yield (58–89%) and excellent diastereoselectivities (>15:1). As part of our program in designing tandem reactions,[104] we carefully optimized this process such that all the steps can be performed in a single flask with the formation of three C–C bonds and stereocenters. The cyclopropyl boronate ester products are valuable building blocks for further elaboration and installation of functional groups via transformations of the B–C bond.

Examined herein is the oxidation of the B–C bond with sodium perborate, which provided the desired trisubstituted α-hydroxycyclopropyl carbinols as single diastereomers in excellent yields. Previous publications document the difficulties encountered by others in the preparation of trisubstituted α-hydroxycyclopropyl carbinols with high diastereoselectivity.[63, 64] These are versatile intermediates in organic synthesis. We developed the highly diastereoselective synthesis of *cis*- and *trans*-2,3-disubstituted cyclobutanones via a facile pinacol-type rearrangement of α-hydroxycyclopropyl carbinols from a common starting material. These cyclobutanones are useful intermediates in organic synthesis and are found in bioactive natural and unnatural products. Using our methods, we have presented the synthesis of quercus lactones A and B.

Given the efficiency and high diastereoselectivity of this approach to cyclopropanol boronate esters, and the ease of formation of α-hydroxycyclopropyl carbinols and *cis*- and *trans*-2,3-disubstituted cyclobutanones, we anticipate this chemistry will be useful in organic synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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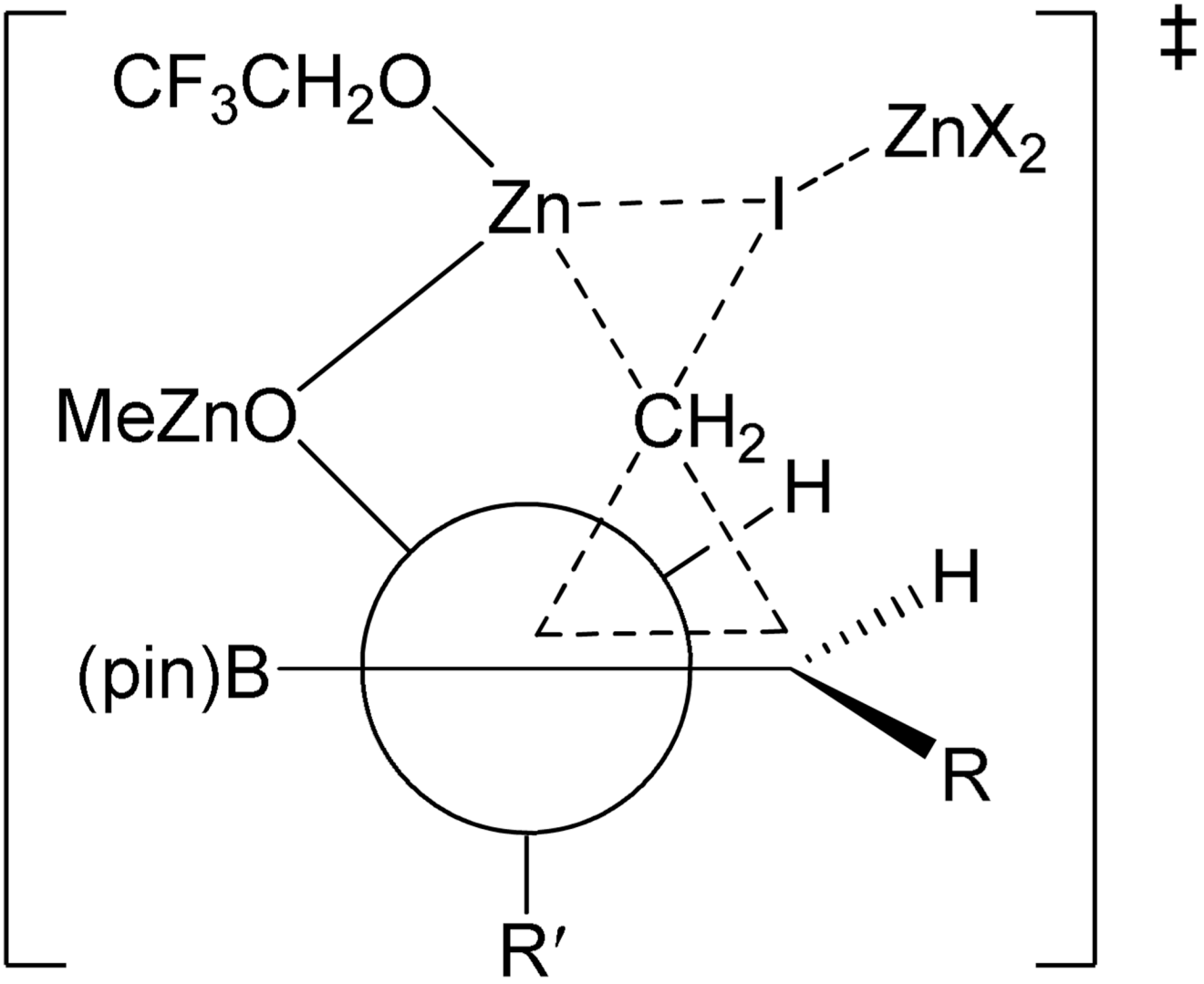


Figure 1.
Proposed Transition State for Diastereoselective Cyclopropanation of B(pin) Substituted Allylic Alkoxides

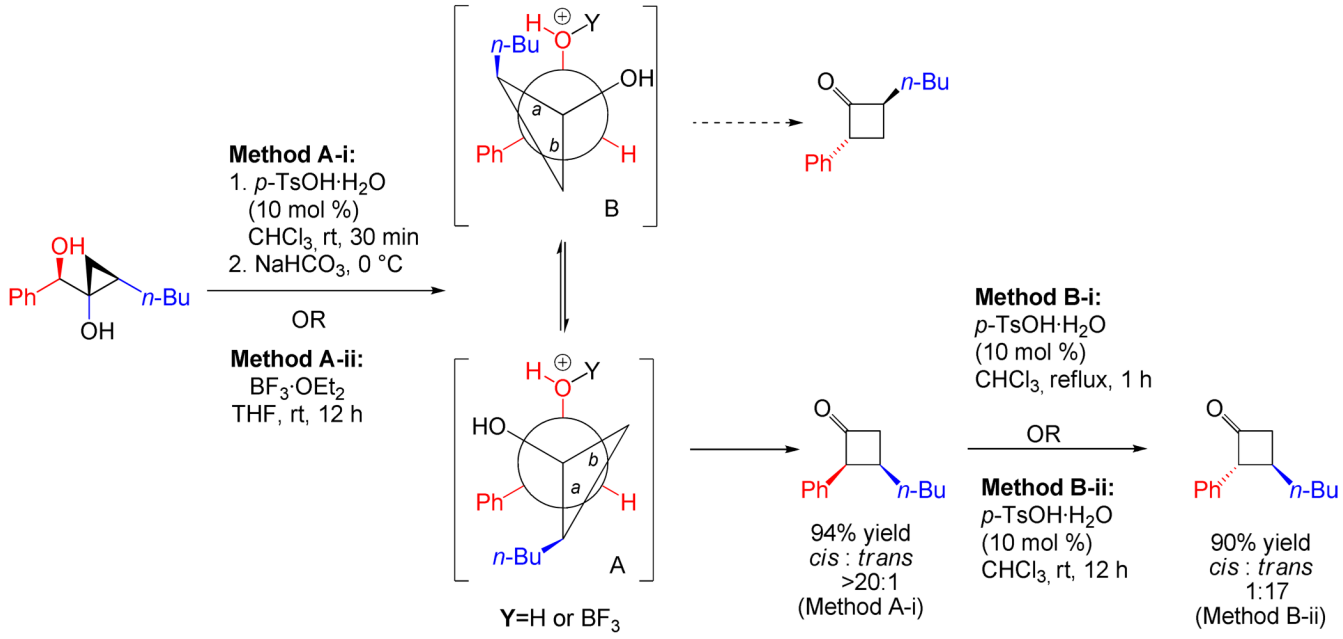


Figure 2.
Optimized Conditions for Synthesis of 2,3-Disubstituted Cyclobutanones via Ring Expansion

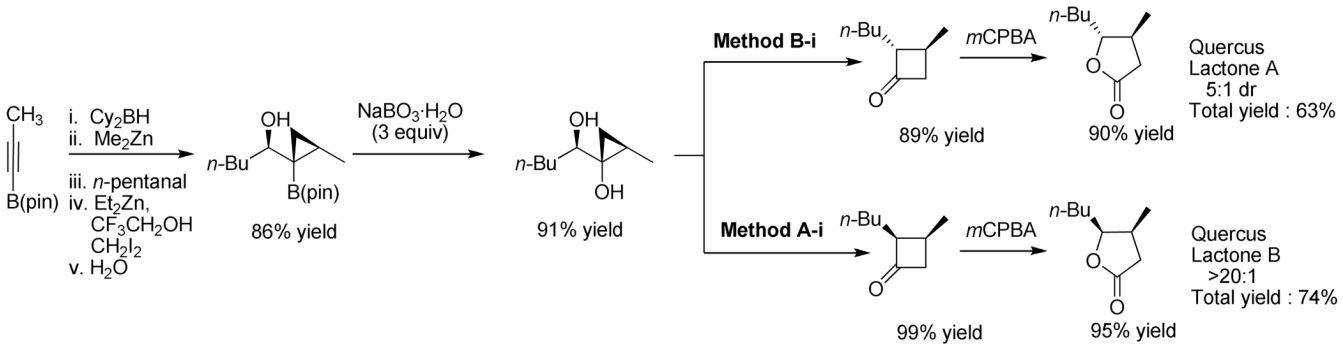
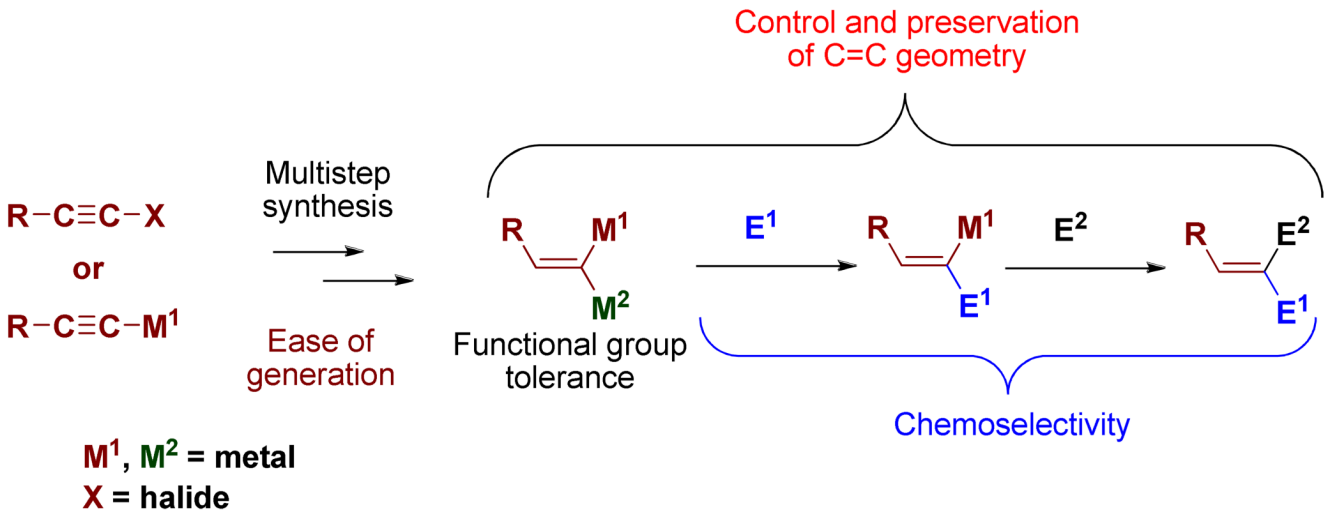
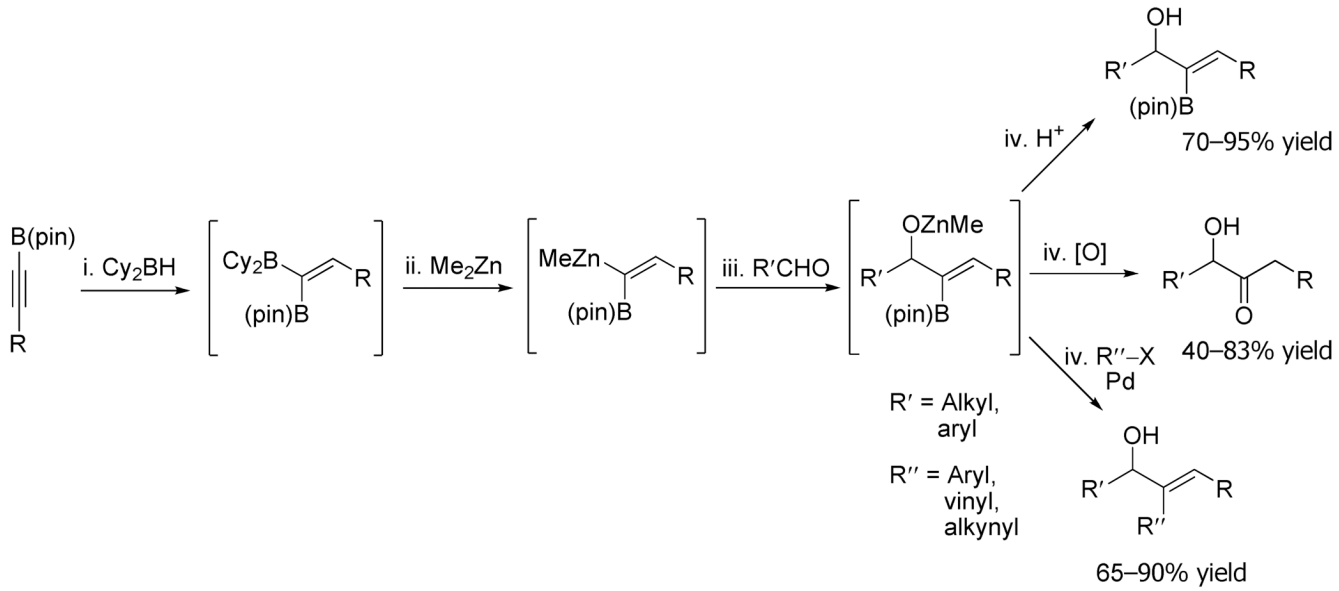


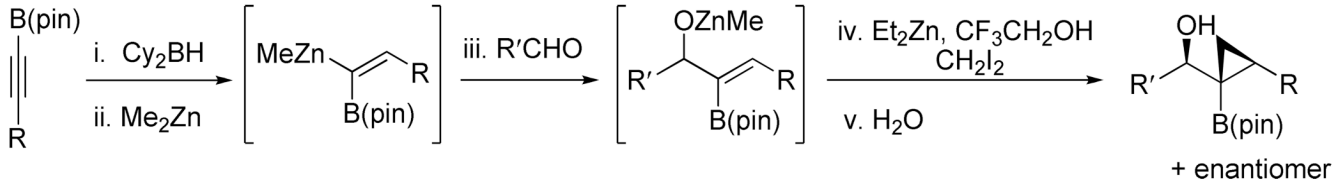
Figure 3.
Synthesis of quercus lactones A and B



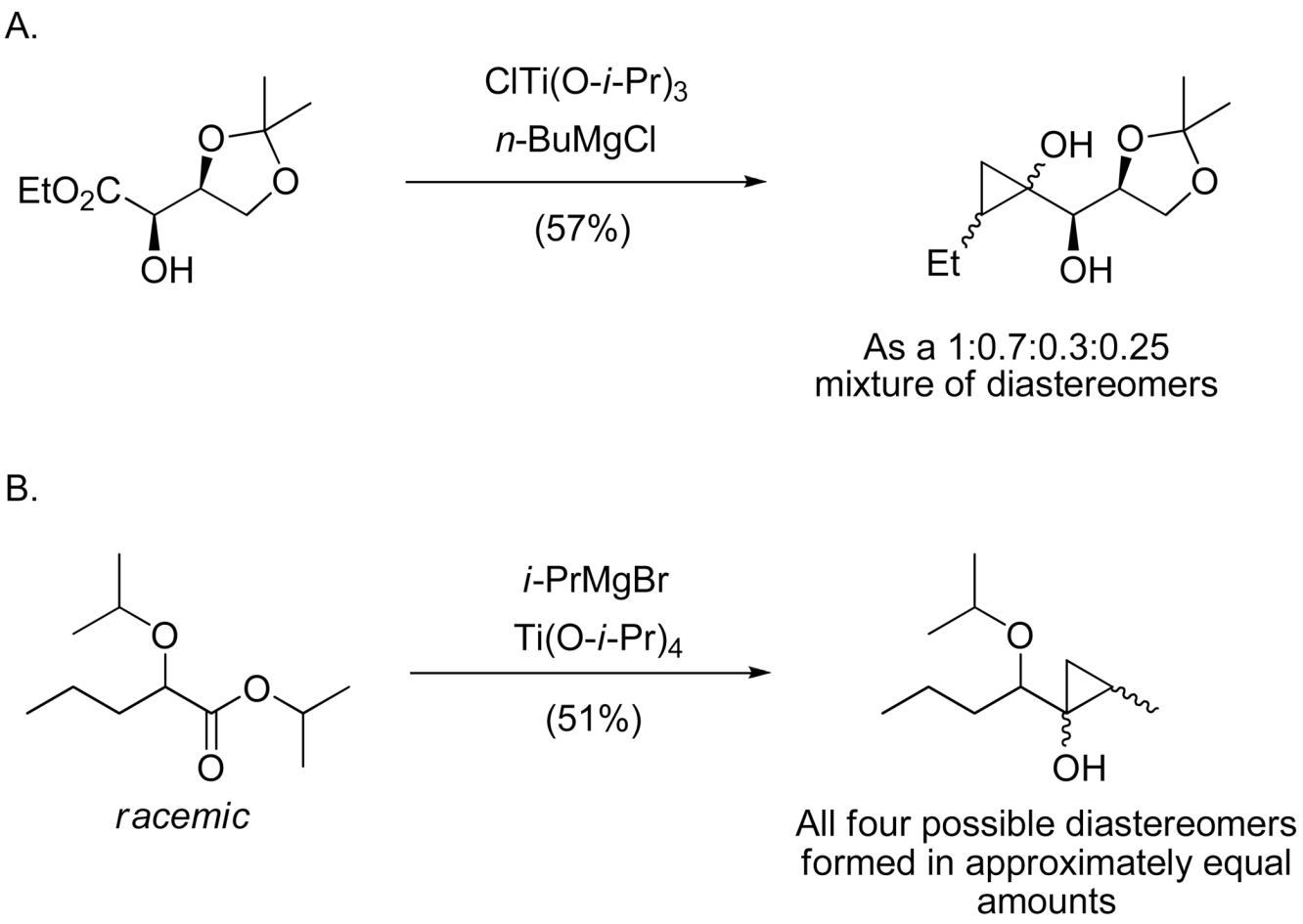
Scheme 1.
Challenges in the Generation and Reactions of 1-Alkenyl-1,1-bimetallics



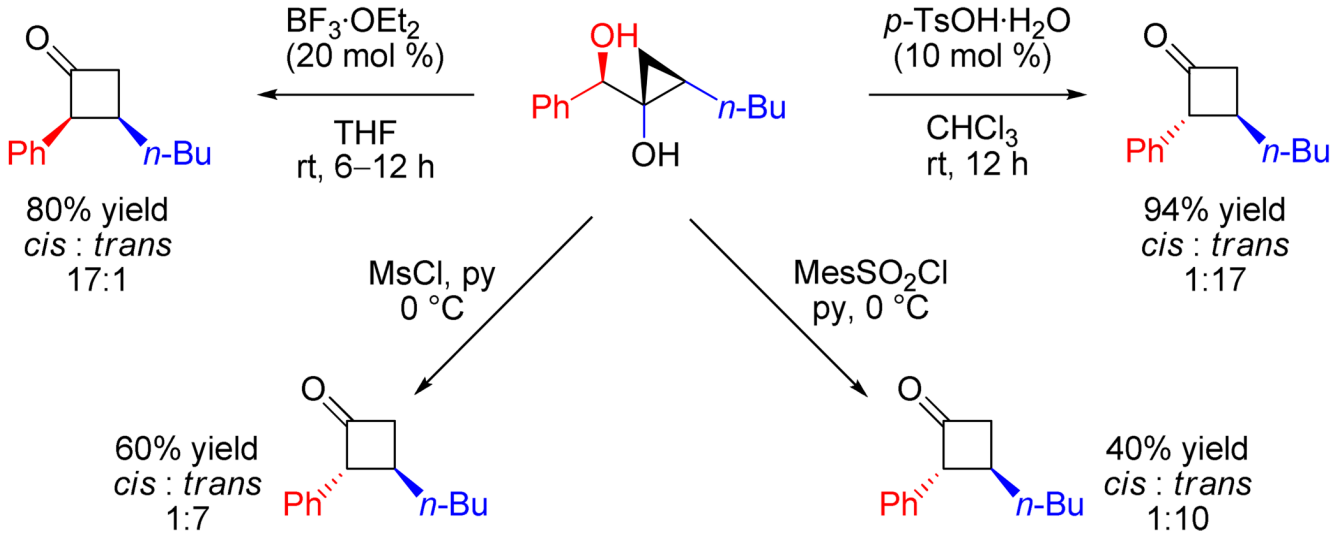
Scheme 2.
Generation and Reactions of 1-Alkenyl-1,1-bimetallics



Scheme 3.
Tandem Carbonyl Addition/Alkoxide-directed Cyclopropanation



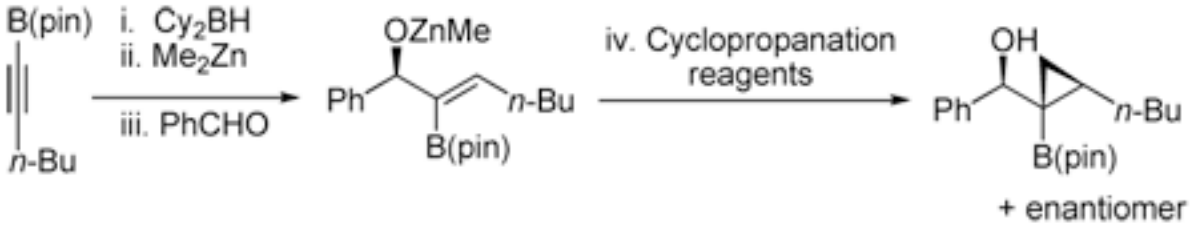
Scheme 4.
Kulinkovich Reaction to Form Trisubstituted Cyclopropanols



Scheme 5.
Pinacol-type Rearrangement of a-Hydroxycyclopropyl Carbinols

Table 1

Optimization of Tandem Carbonyl Addition/Cyclopropanation of 1-Alkenyl-1,1-heterobimetallics



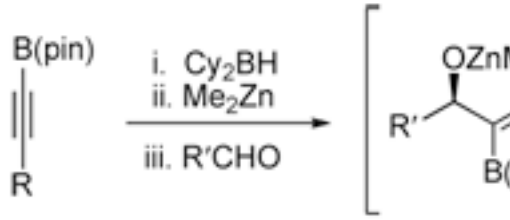
entry	reagents (equiv)	active intermediate	temp. (°C)	conv. (% yield)[a]
1	Et_2Zn (5) CH_2I_2 (5)	$EtZnCH_2I$	rt	40
2	I_2 (2.5) Et_2Zn (2.5) CH_2I_2 (2.5)	$IZnCH_2I$	rt	<10
3	Et_2Zn (5) CH_2I_2 (10)	$Zn(CH_2I)_2$	rt	95
4	Et_2Zn (5) CH_2I_2 (10)	$Zn(CH_2I)_2$	40	100 (62)
5	Et_2Zn (5) CF_3COOH (5) CH_2I_2 (5)	$CF_3COOZnCH_2I$	rt	80
6	Et_2Zn (5) CF_3CH_2OH (5) CH_2I_2 (5)	$CF_3CH_2OZnCH_2I$	rt	75
7	Et_2Zn (5) CF_3CH_2OH (5) CH_2I_2 (5)	$CF_3CH_2OZnCH_2I$	rt	100 (72)[b]

[a] Isolated yields.

[b] All volatiles are removed in vacuo after the addition step. Subsequent cyclopropanation is conducted using 2M Et_2Zn solution in toluene.

Table 2

Stereoselective Synthesis of Cyclopropyl Boronate Esters via Tandem Carbonyl Addition/Cyclopropanation of 1-Alkenyl-1,1-heterobimetallics



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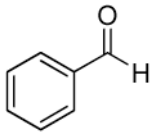
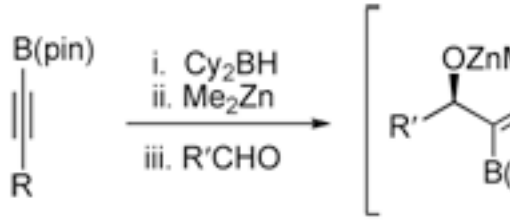
1	



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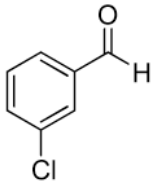
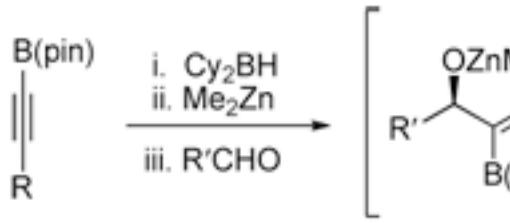
2	



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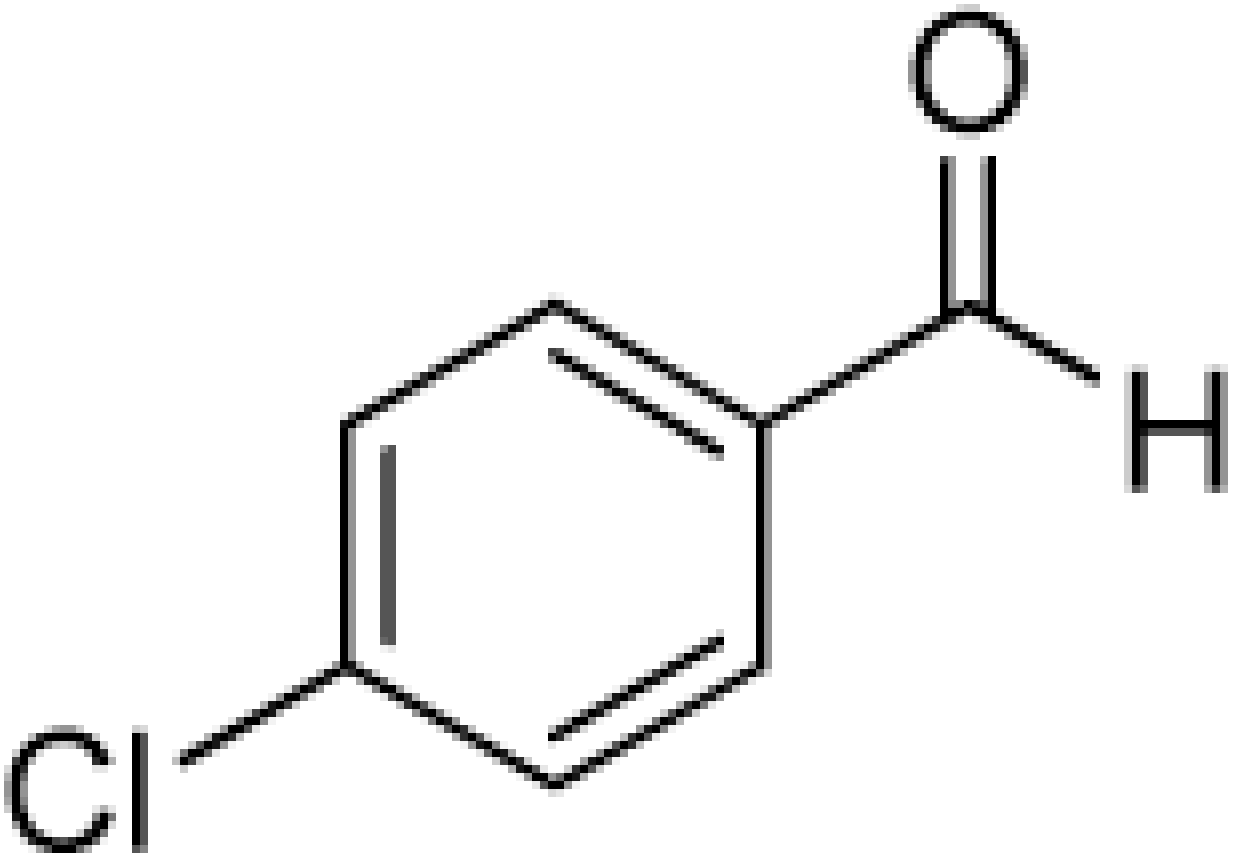
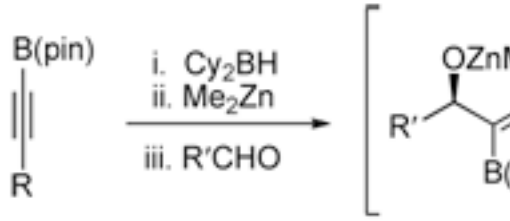
3	



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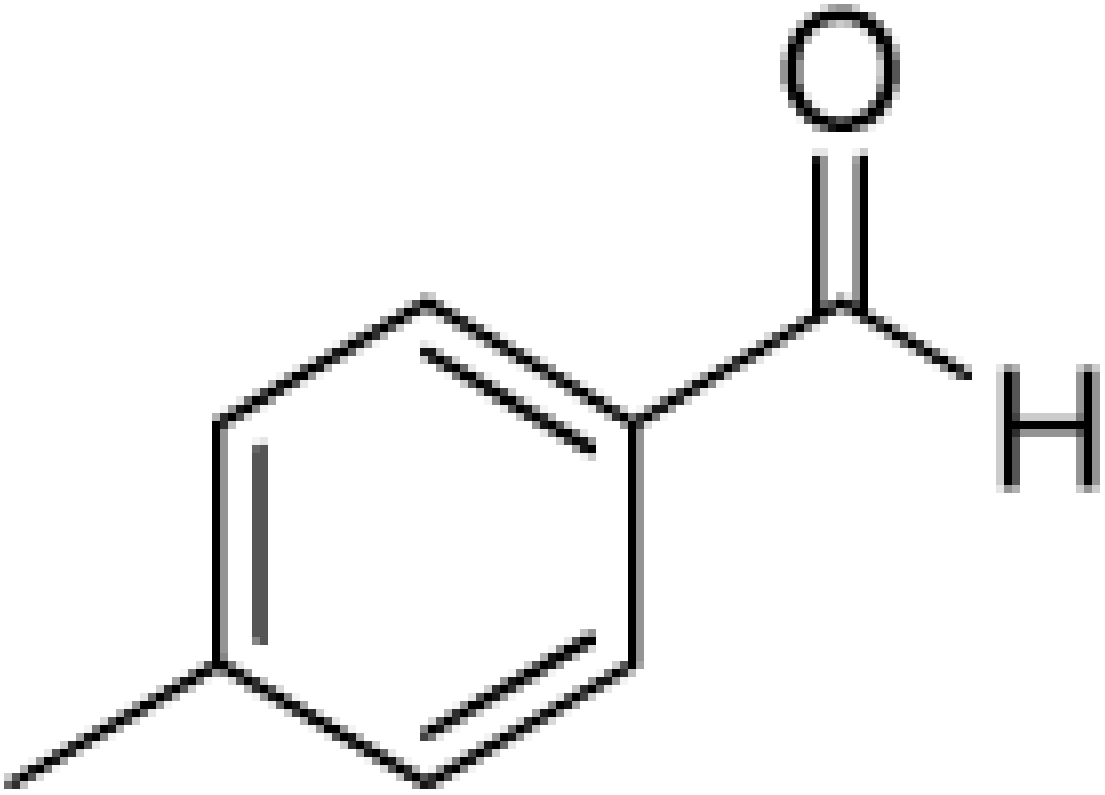
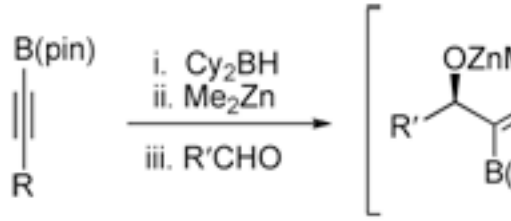
4	



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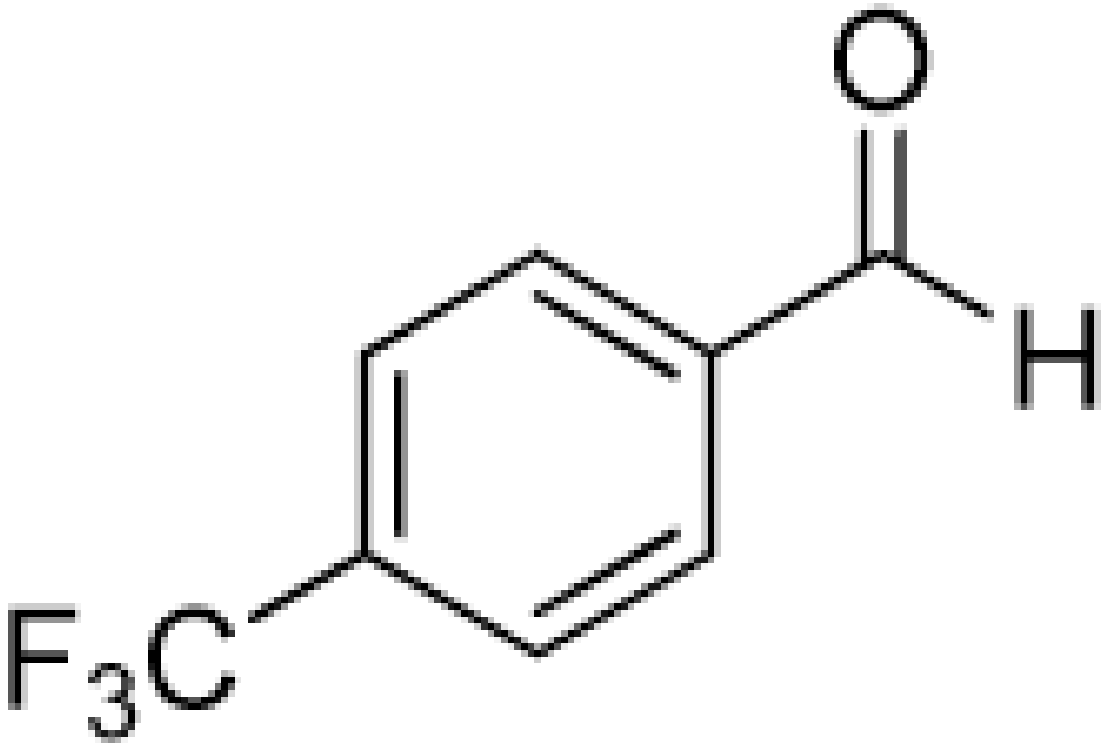
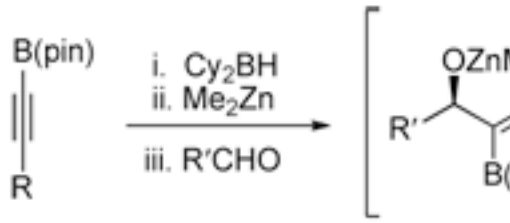
5	



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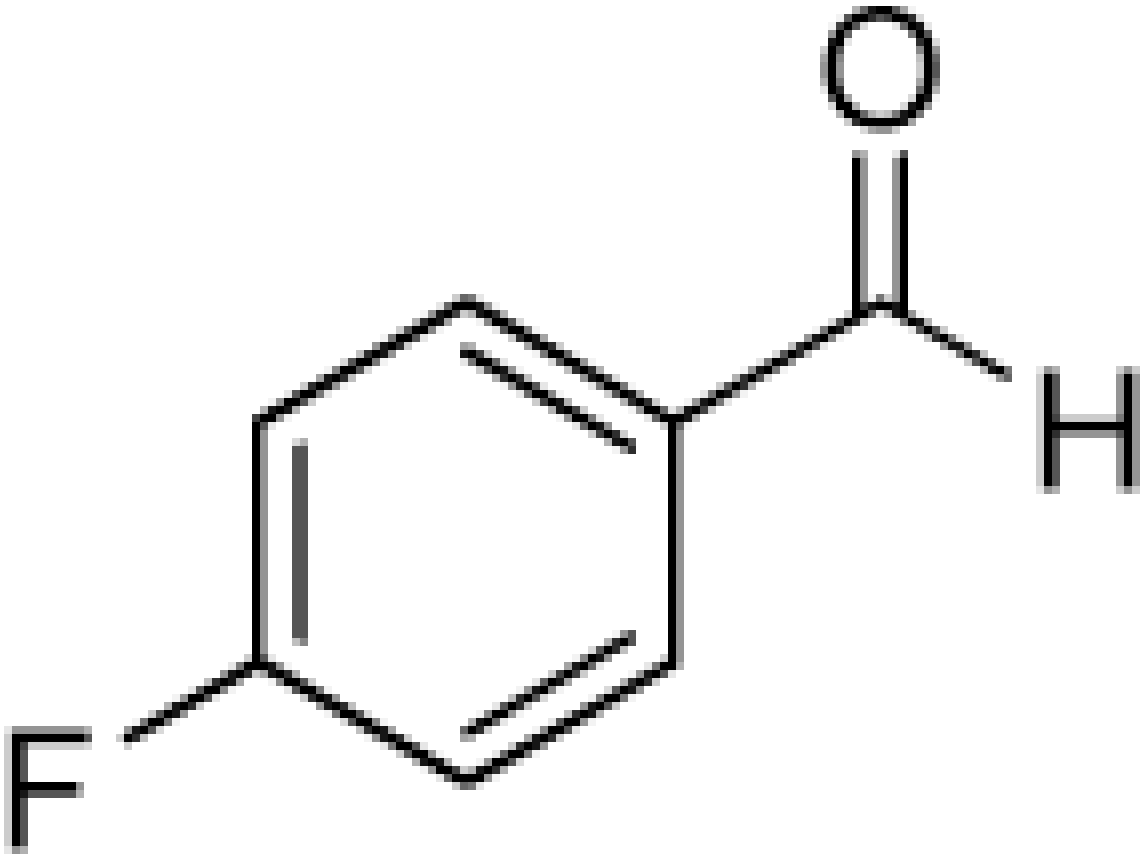
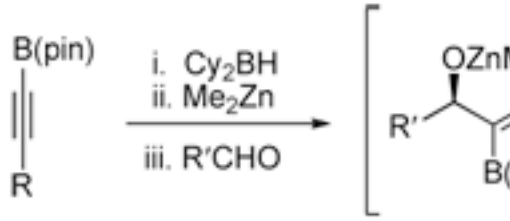
6	



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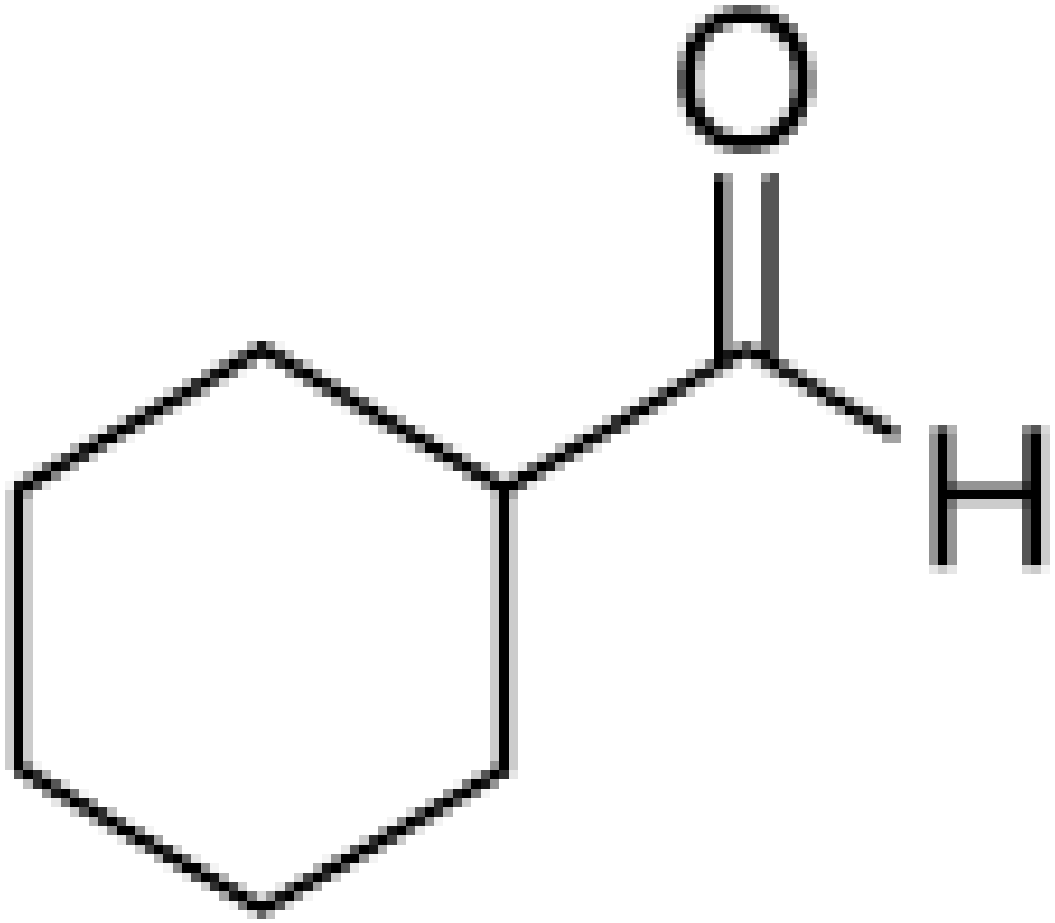
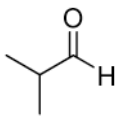
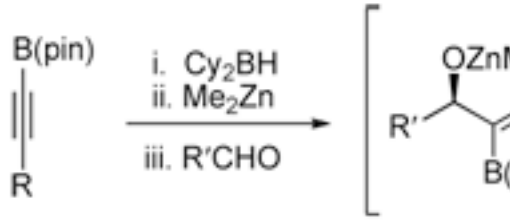
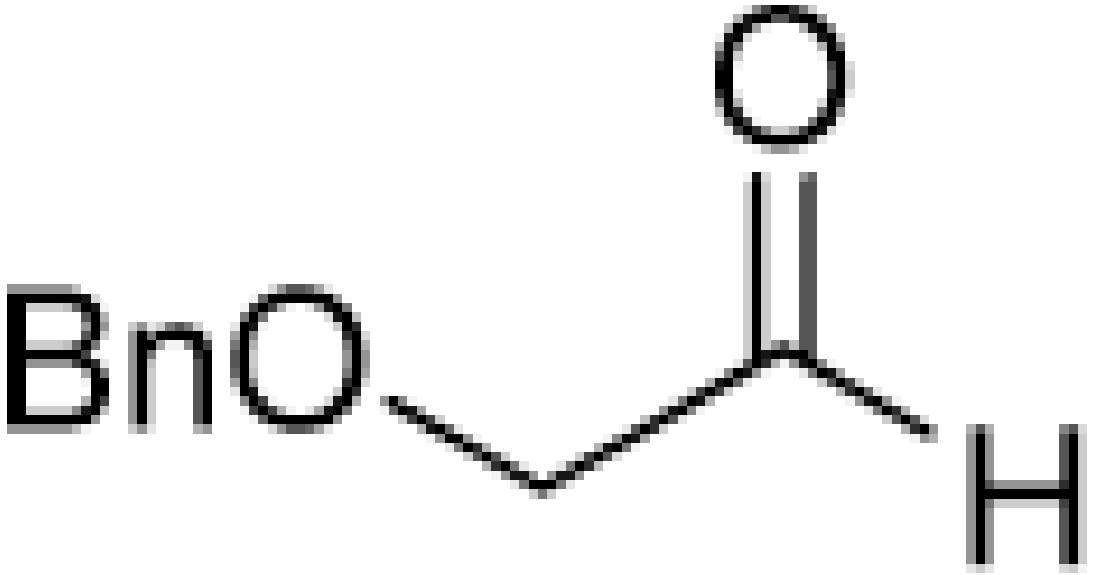
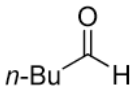
7	
8	

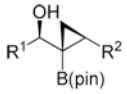


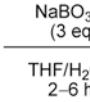
entry	aldehydes
9	
10	

[a] Isolated yields

Table 3

Stereoselective Synthesis of Trisubstituted α-Hydroxycyclopropyl Carbinols





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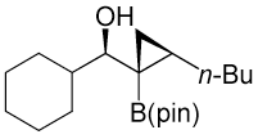
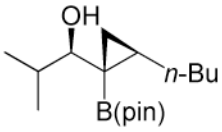
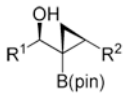
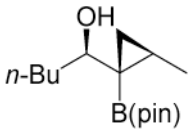
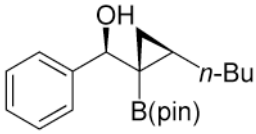
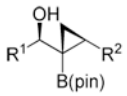
1	
2	

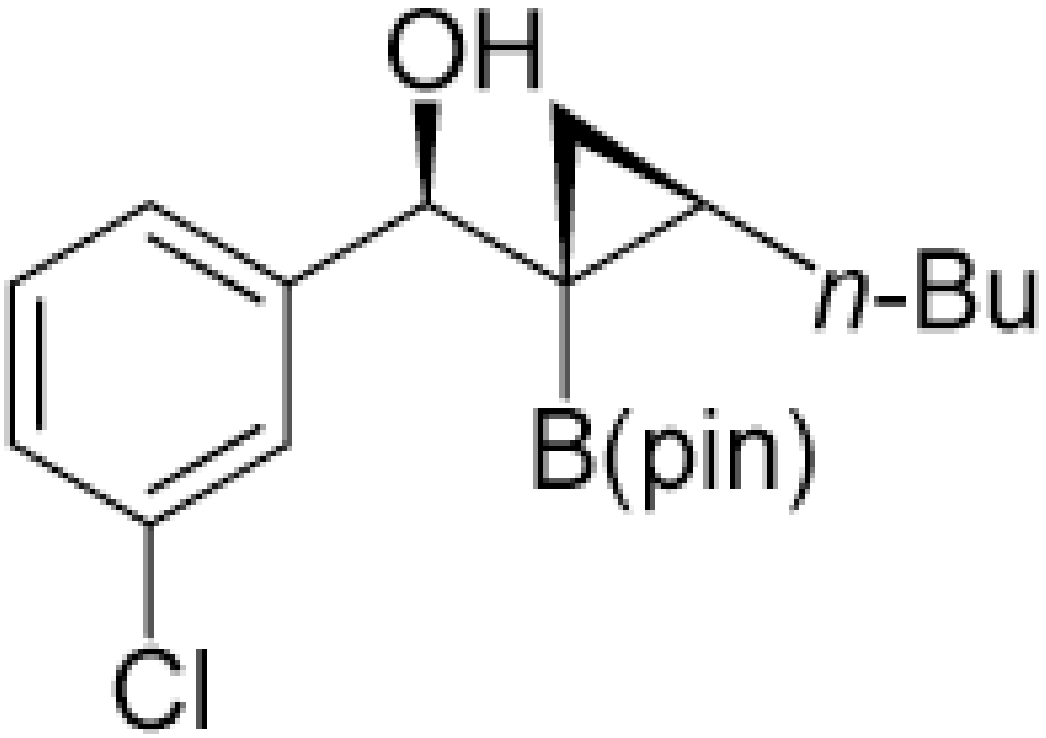
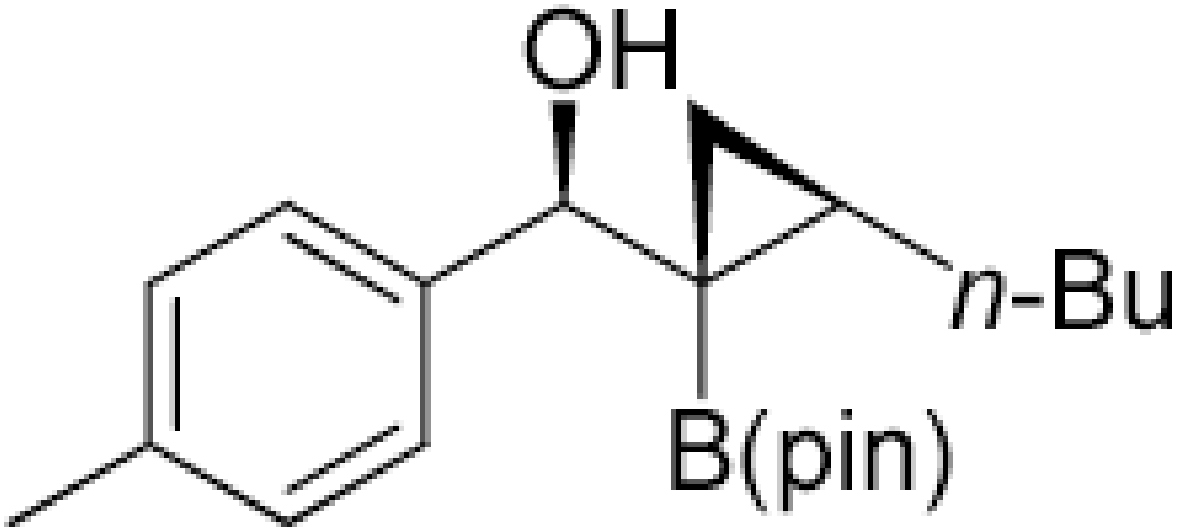


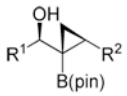
NaBO3
(3 eq
THF/H2
2–6 h

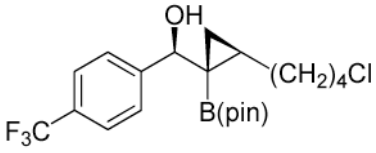
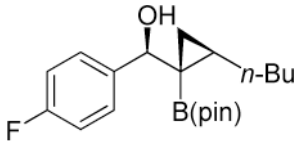
entry	cyclopropyl boronate ester
3	
4	



NaBO3
(3 eq
THF/H2
2–6 h

entry	cyclopropyl boronate ester
5	
6	

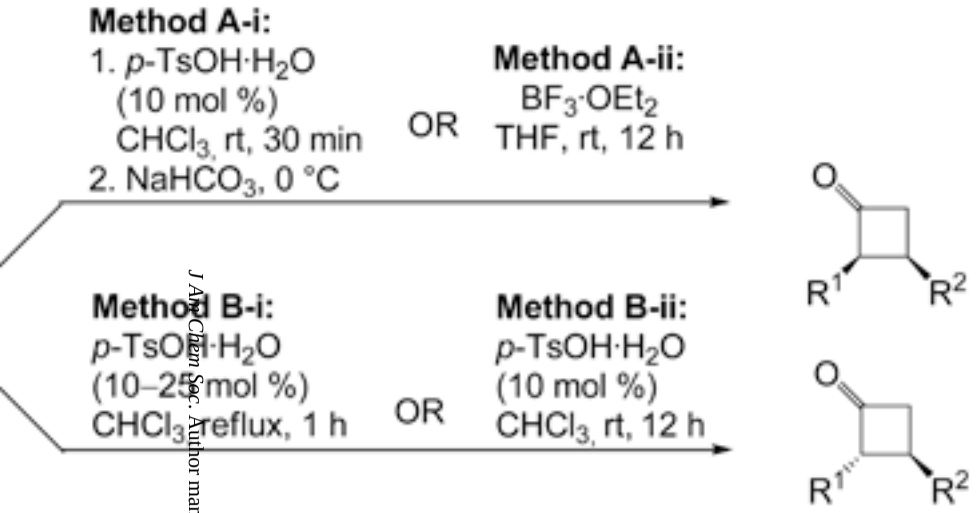


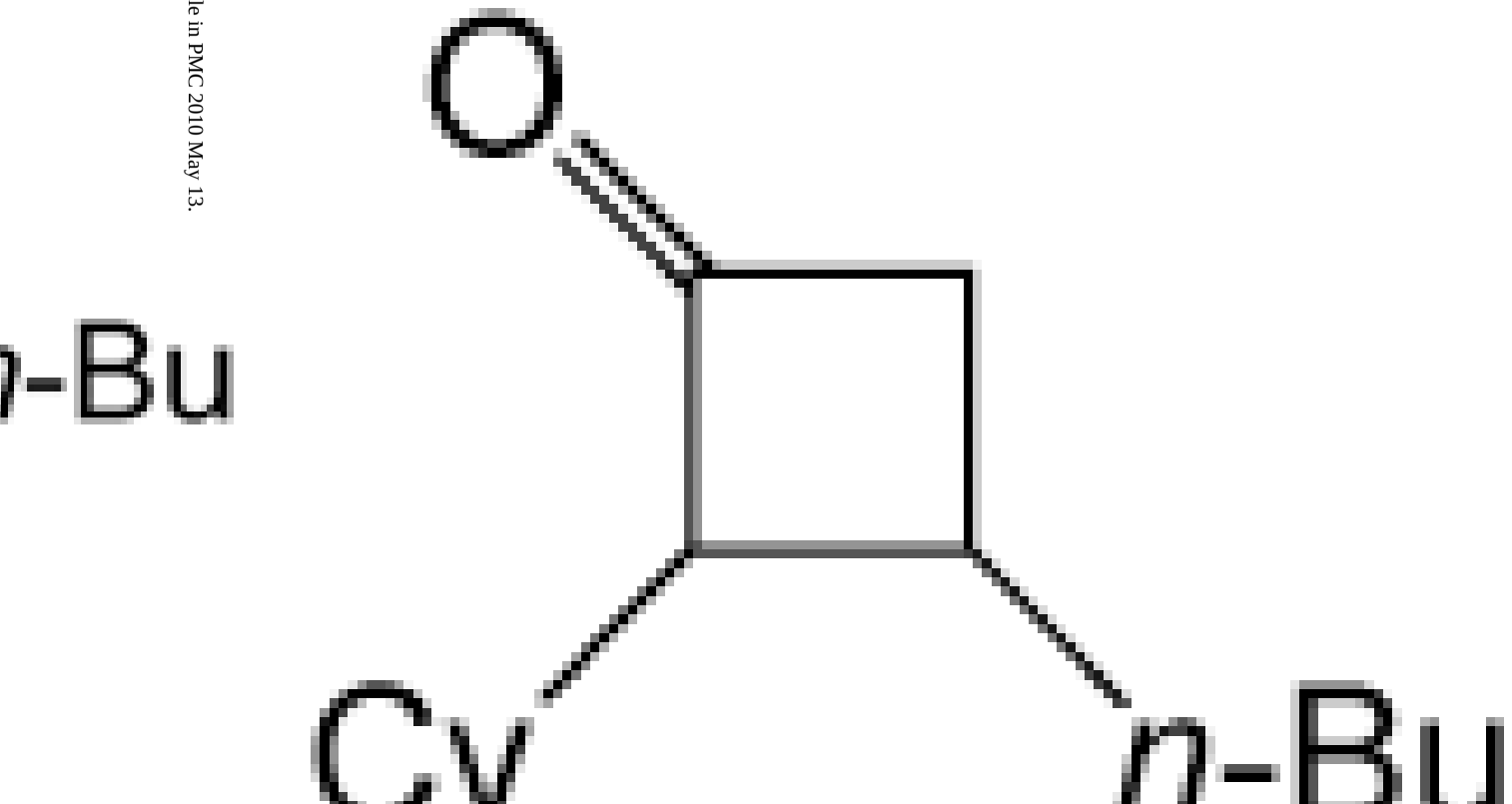
entry	cyclopropyl boronate ester
7	
8	

[a] Only one diastereomer detected by ^{1}H NMR.

[b] *Syn* stereochemistry of α-hydroxycyclopropyl carbinols established by single crystal X-ray diffraction.

Table 4



cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
	A-i B-ii	>20:1 >1:20	94 90

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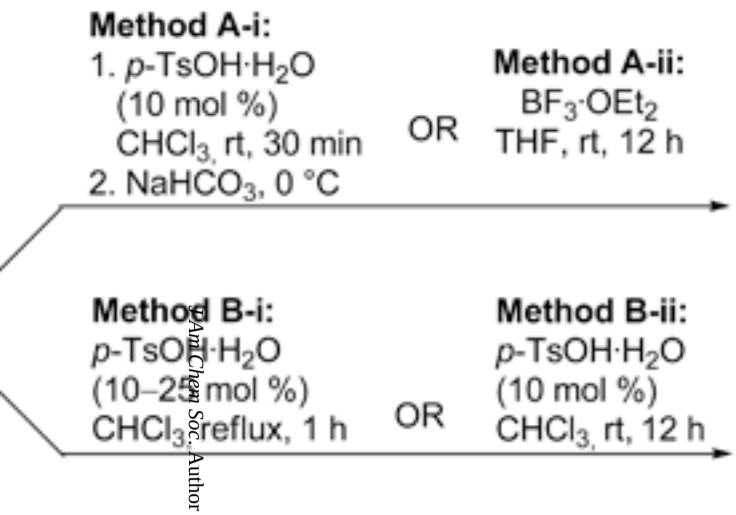
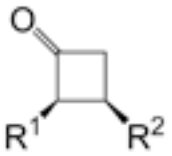
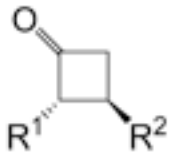
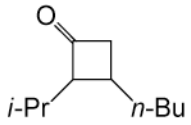






cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
	A-i	>20:1	95
	B-i	>1:20	80

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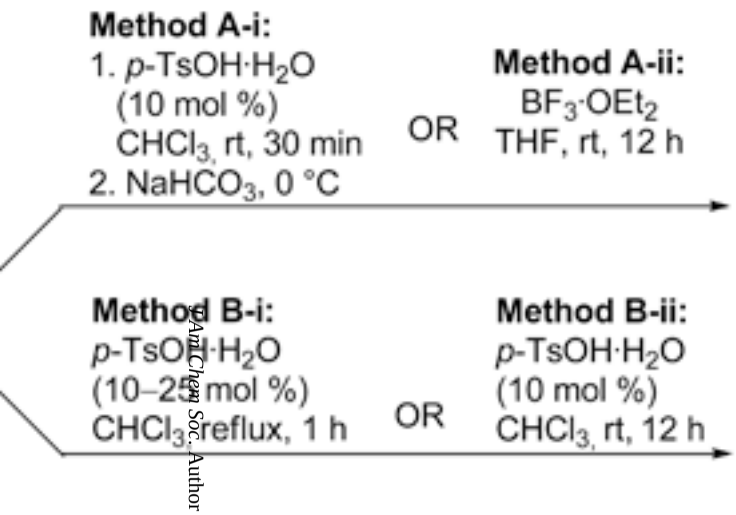
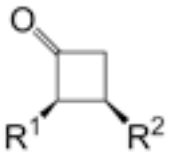
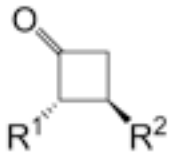
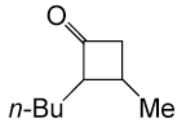
Bu







cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
	A-i	>20:1	99
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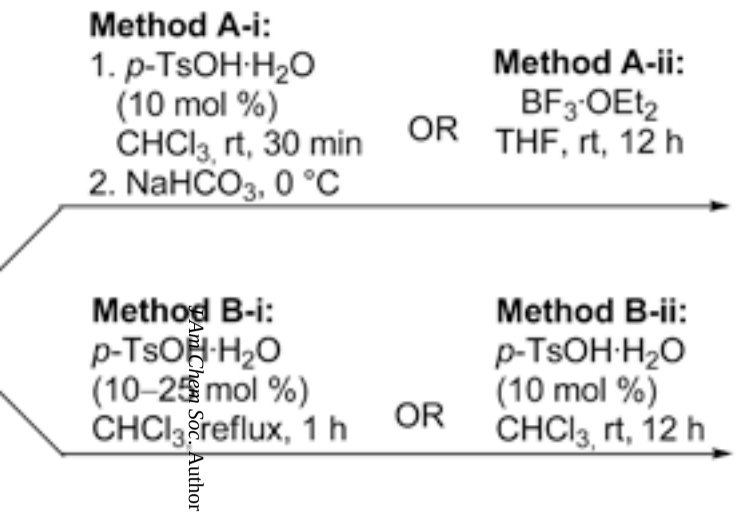
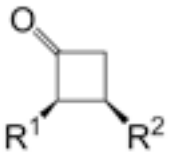
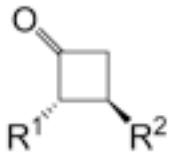
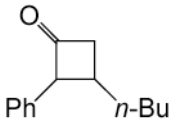






cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
	A-i	>20:1	99
	B-ii	1:17	90

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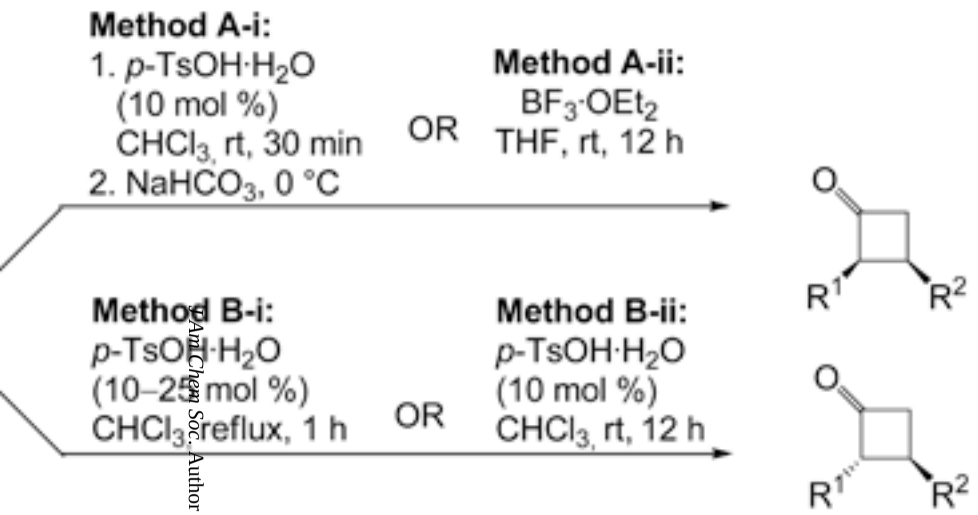
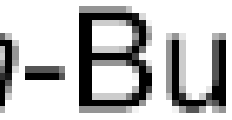
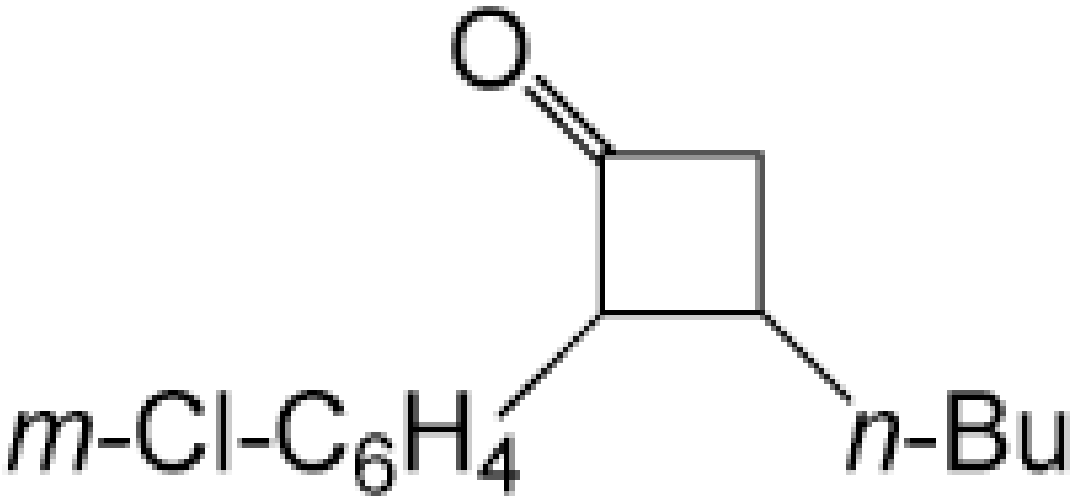


	cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
				
		A-i B-i	17:1 1:17	99 85

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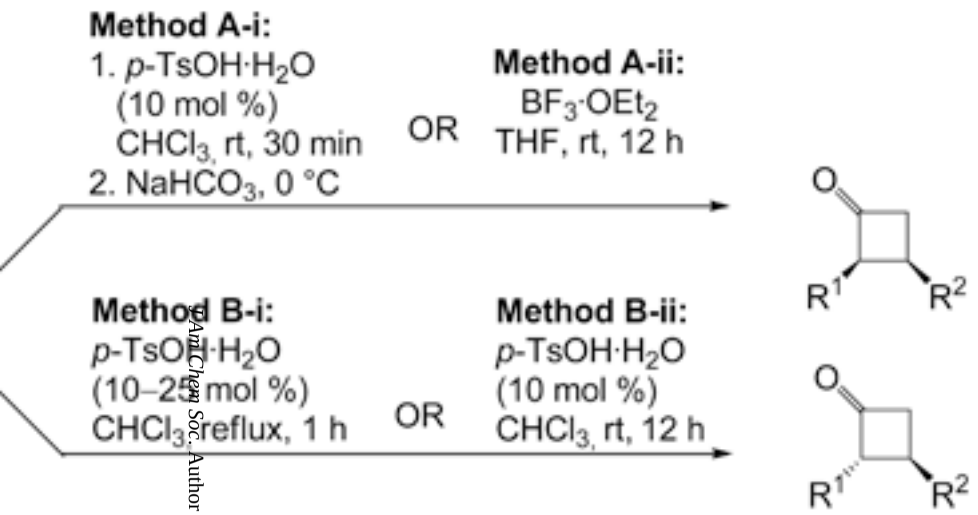
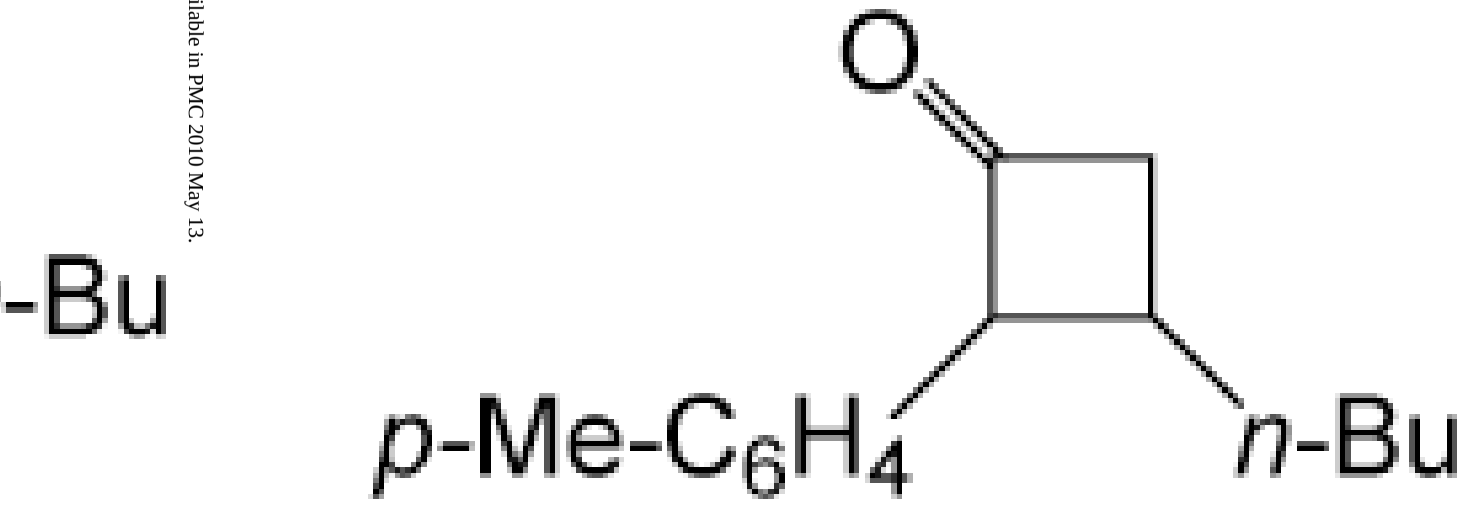


cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
	A-i B-i	>20:1 1:20	94 77

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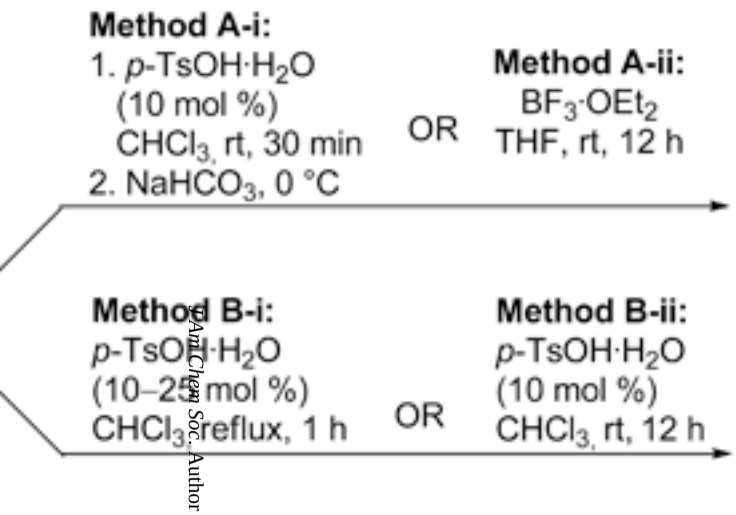
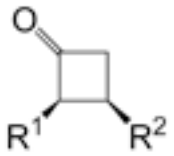
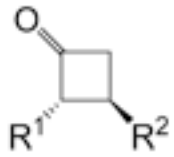
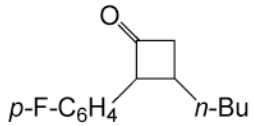






	cyclobutanones	Method	*cis:trans*[a]	isolated yield (%)
		A-i B-i	>20:1 20:1	99 80