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Catalytic enantioselective synthesis of benzocyclobutenols and cyclobutanols *via* a sequential reduction/C–H functionalization†

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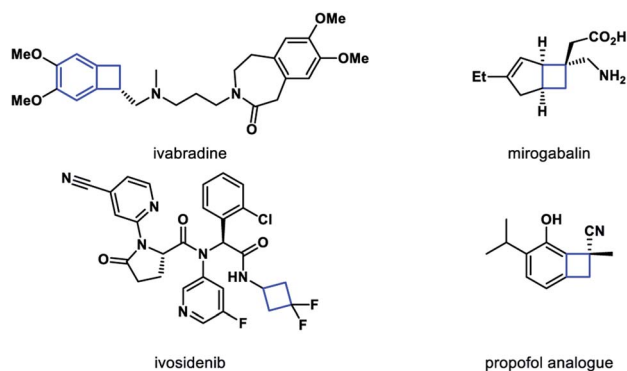
We report here a sequential enantioselective reduction/C–H functionalization to install contiguous stereogenic carbon centers of benzocyclobutenols and cyclobutanols. This strategy features a practical enantioselective reduction of a ketone and a diastereospecific iridium-catalyzed C–H silylation. Further transformations have been explored, including controllable regioselective ring-opening reactions. In addition, this strategy has been utilized for the synthesis of three natural products, phyllostoxin (proposed structure), grandisol and fragranol.

Molecules with inherent ring strain have gained considerable interest in the synthetic community.¹ Among them, four-membered ring molecules have been recognized as powerful building blocks in organic synthesis.² Driven by ring strain releasing, the reactions of carbon–carbon bond cleavage have been extensively studied in recent years.³ Meanwhile, cyclobutane motifs represent important structural units in natural product and bioactive molecules as well (Scheme 1).⁴ Therefore, a general and robust method to constitute four-membered ring derivatives is of great value, especially in an enantiomerically pure form.⁵

[2 + 2]-Cycloaddition⁶ and the skeleton rearrangement reaction⁷ are two primary methods to prepare chiral cyclobutane derivatives. Recently, the precision modification of four-membered ring skeletons to access enantioenriched cyclobutane derivatives has attracted emerging attention. Several strategies have been developed, including allylic alkylation,⁸ α -functionalization,⁹ conjugate addition¹⁰ and C–H functionalization¹¹ of prochiral or racemic cyclobutane derivatives (Scheme 2a).¹² However, the enantioselective synthesis of chiral benzocyclobutene derivatives is still underdeveloped.¹³ Although two efficient palladium-catalyzed C–H activation strategies have been developed by Baudoin¹⁴ and Martin¹⁵ groups *via* similar intermediate five-membered palladacycles, no enantioenriched benzocyclobutene derivative has been prepared by employing the above two methods. In 2017, Kawabata reported an elegant

example of asymmetric intermolecular α -arylation of enantioenriched amino acid derivatives to afford benzocyclobutenones with tetrasubstituted carbon *via* memory of chirality (Scheme 2b).¹⁶ In 2018, Zhang reported an iridium-catalyzed asymmetric hydrogenation of α -alkylidene benzocyclobutenones in good enantioselectivities (3 examples, 83–88% ee).^{12c} To the best of our knowledge, there is no report on enantioselective synthesis of benzocyclobutene derivatives with all-carbon quaternary centers.

In line with our continued interest in precision modification of four-membered ring skeletons,^{9d,10c,12a} we initiated our studies on the synthesis of chiral benzocyclobutenes *via* enantioselective functionalization of highly strained benzocyclobutenones. It is well known that benzocyclobutene derivatives are labile to undergo a ring-opening reaction to release their inherent ring strains.¹⁷ Therefore, it is a challenging task to modify the benzocyclobutenone and preserve the four-membered ring skeleton at the same time. We envisioned that

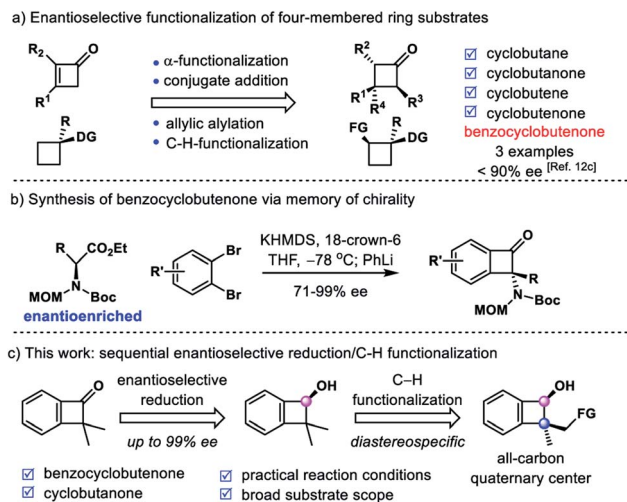


Scheme 1 Representative cyclobutane-containing bioactive molecules.

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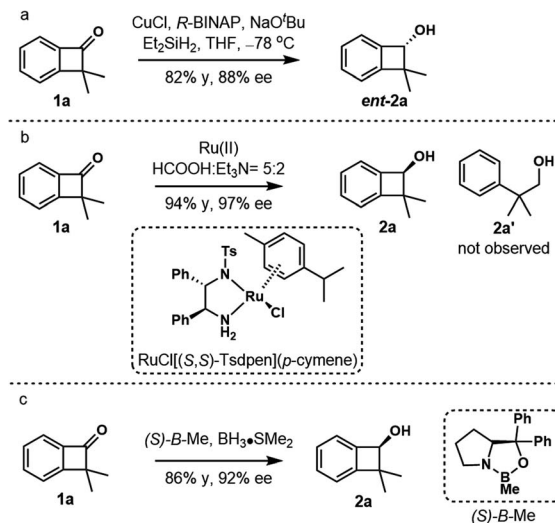
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Scheme 2 Asymmetric synthesis of cyclobutanes and their derivatives. (a) Enantioselective functionalization of four-membered ring substrates. (b) Synthesis of chiral benzocyclobutenone via memory of chirality. (c) This work: sequential enantioselective reduction/C-H functionalization.

a carbonyl group directed C-H functionalization¹⁸ of the *gem*-dimethyl group could furnish enantioenriched α -quaternary benzocyclobutenones (Scheme 2c). This could be viewed as an alternative approach to achieve the alkylation of benzocyclobutenone, which was otherwise directly inaccessible using enolate chemistry through the unstable anti-aromatic intermediate.¹⁹ In addition, a highly regioselective C-H activation would be required to functionalize the methyl group instead of the aryl ring. Here we report our work on sequential enantioselective reduction and intramolecular C-H silylation to provide enantioenriched benzocyclobutenols and cyclobutanols with all-carbon quaternary centers. The excellent diastereoselectivity and regioselectivity of silylation were attributed to rigid structural organization of the 4/5 fused ring. Furthermore, this strategy has been utilized to accomplish the total synthesis of natural products phyllostoxin (proposed structure), grandisol and fragranol.

We commenced our studies with enantioselective reduction of readily prepared dimethylbenzocyclobutenone **1a** (Scheme 3).^{15,20} Surprisingly, enantioselective reduction of the carbonyl group of cyclobutanone derivatives received little attention. The first reduction of parent benzocyclobutenone was studied in 1996 by Kündig using chlorodiisopinocampheylborane²¹ or chiral oxazaborolidines (CBS reduction),²² and only moderate enantioselectivity (44–68% ee) was obtained.²³ Although copper-catalyzed asymmetric hydrosilylation of benzocyclobutenone **1a** using CuCl/(*R*)-BINAP gave the benzocyclobutenol *ent*-**2a** in 88% ee, optimization of ligands gave no further improvement (Scheme 3a, see Tables S1–S4† for details).²⁴ Gladly, excellent enantioselective reduction could be achieved in 94% yield and 97% ee under Noyori's asymmetric transfer hydrogenation conditions (Scheme 3b, conditions A, RuCl[(*S,S*)-Tsdpen](*p*-cymene)).²⁵ The product **2a** showed remarkable stability and no ring-opening byproduct **2a'** was observed. The reduction of



Scheme 3 Enantioselective reduction of benzocyclobutenone **1a**. (a) Copper hydride reduction. (b) Ru-catalyzed asymmetric transfer hydrogenation. (c) CBS reduction.

parent benzocyclobutenone was examined under conditions A, and benzocyclobutenol was obtained in 90% yield and 81% ee. Apparently, the steric influence imposed by the α -dimethyl group enhanced the enantioselectivity of the reduction. Similarly, the CBS reduction ((*S*)-B-Me) of benzocyclobutenone **1a** gave better results compared with parent benzocyclobutenone, affording the product **2a** in 86% yield and 92% ee (Scheme 3c).

Table 1 Enantioselective reduction of benzocyclobutenones^a

 2a 94% y, 97% ee	 2b , R = Me 84% y, 95% ee 2c , R = Cl 93% y, 88% ee 2d , R = F 80% y, 89% ee	 2e , R = OMe 56% y, 94% ee 2f , R = Me ^b 77% y, 98% ee
 2g 96% y, 93% ee ^b	 2h 49% y, 89% ee ^b	 2h' 18% y
 2i 93% y, 99% ee ^b	 2j , R = Me 91% y, 99% ee ^b 2k , R = OMe 91% y, 99% ee ^b	 2l , R = Me 99% y, 99% ee ^b 2m , R = OMe 97% y, 99% ee ^b
 2n 92% y, 99% ee		

^a Conditions A: **1a** (0.5–2.0 mmol), RuCl[(*S,S*)-Tsdpen](*p*-cymene) (1–2 mol%), HCOOH/Et₃N (5/2), rt. All results are corrected to the (*S*)-catalyst. The ee values were determined by HPLC analysis; see the ESI for more details. ^b (*S,S*)-Ts-DENEb (1–2 mol%) was used, rt or 60 °C.

We then examined the substrate scope of the reduction reaction (Table 1). A variety of substituted benzocyclobutenones were tolerated, giving the corresponding benzocyclobutenols **2b–2n** in 56–99% yield and 88–99% ee. Notably, benzocyclobutenones with electron-rich substitutions (**2e**, **2f** and **2i–2n**) showed much lower reactivity towards reduction, and thus a more reactive catalyst (*S,S*)-Ts-DENEB²⁶ was chosen to improve the yield and enantioselectivity. Besides, benzocyclobutenol **2g** with nitro substitution could be obtained in 96% yield and 93% ee. Treatment of pyrrolidinyl substituted benzocyclobutenone **1h** with catalyst (*S,S*)-Ts-DENEB afforded desired product **2h** in 49% yield and 89% ee, together with ring-opening product **2h'** (18%).

3,3-Disubstituted cyclobutanones were also explored (Table 2). Using catalyst (*S,S*)-Ts-DENEB, the reaction of 2,2-dimethyl-3,3-diphenylcyclobutanone **3a** gave cyclobutanol **4a** only in 44% ee. After optimization, we were glad to find that oxazaborolidine (*S*)-B-Me turned out to be the best catalyst, and cyclobutanol **4a** could be obtained in 93% yield and 91% ee (conditions B). The reduction of cyclobutanone **3b** gave alcohol **4b** in excellent yield and enantioselectivity as well. Interestingly, racemic cyclobutanones underwent efficient optical resolution to give the corresponding two diastereomers, both with high enantiomeric purity. Treatment of cyclobutanones **3c–3h** with (*S*)-B-Me and $\text{BH}_3 \cdot \text{Me}_2\text{S}$ provided the corresponding *cis*- and *trans*-cyclobutanols **4c–4h** in a nearly 1 : 1 diastereomeric ratio and 91–99% ee. In addition, CBS reduction of bicyclic cyclobutanones was also examined. The reaction of **3i** afforded *trans*-

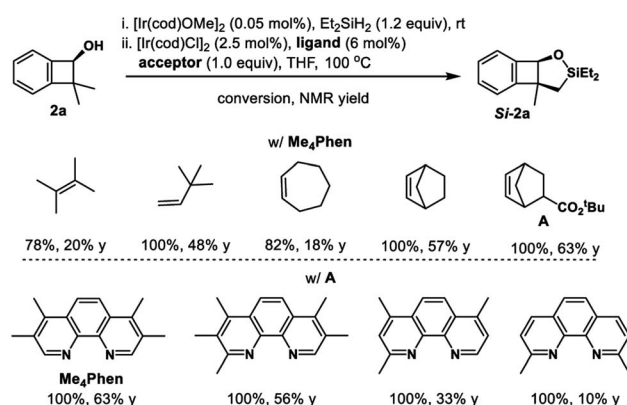
4i in 29% yield and 98% ee, along with *cis*-**4i** in 56% yield and 44% ee. And reduction with (–)-Ipc₂BCl afforded *ent-trans*-**4i** in 34% yield and 97% ee, along with *ent-cis*-**4i** in 42% yield and 70% ee. Dess–Martin periodinane oxidation of *ent-trans*-**4i** (97% ee), followed by selective reduction with *L*-selectride gave *cis*-**4i** as a single product in 99% yield and 96% ee. The reaction of **3j** gave similar results, and enantioenriched cyclobutanols *cis*-**4j** could be furnished in 78% yield and 97% ee from *ent-trans*-**4j** (98% ee) following the above oxidation–reduction procedure. The absolute configurations of **2a**, *ent*-**2j** and *trans*-**4i** were unambiguously determined by single-crystal X-ray diffraction analysis of their corresponding nitrobenzoate derivative.²⁷

Inspired by powerful and reliable directed C–H silylation chemistry pioneered by Hartwig,²⁸ we envisioned that the transition-metal catalyzed intramolecular C–H silylations of the above alcohols would provide a single diastereomer owing to rigid structural organization. The challenges here are the control of regioselectivity in the cyclization step and inhibition of the ring-opening pathway. Benzocyclobutenol **2a** was chosen as a model substrate to study this intramolecular C–H silylation. The transition-metal catalyst system and alkene acceptors were screened (Scheme 4, see Tables S5–S9† for details). Acceptor norbornene (nbe) derivative **A** gave the optimal yield in the cyclization step (63% NMR yield), and other phenanthroline ligands gave inferior results. The reaction showed remarkable regio- and diastereoselectivity; no silylation of the arene was detected. With optimal intramolecular silylation conditions in hand, sequential hydroxysilylation/C–H silylation/phenyllithium addition reaction of **2a** provided desired product **5a** in 56% overall yield without any obvious erosion of enantiomeric purity (Table 3, conditions C). Then the reactions of the above enantioenriched benzocyclobutenols **2b–2m** were examined. The corresponding products **5b–5f** and **5h–5m** could be obtained in 30–83% overall yield without obvious enantiomeric purity erosion (96–99% es). However, the reaction of **2g** gave no expected product **5g**. Notably, we did observe ring-opening byproduct **5e'** (14% yield) when using $[\text{Ir}(\text{COD})\text{OMe}]_2$ as a catalyst and NBE as a hydrogen acceptor in the reaction of **4e**. This byproduct was efficiently suppressed under optimal conditions, giving product **5e** in 52% yield. Besides the

Table 2 Enantioselective reduction of cyclobutanones **3**^a

 4a , R = Ph 93% y, 91% ee 4b , R = Me 93% y, 95% ee	 <i>cis</i> - 4c , Ar = Ph 48% y, 92% ee <i>cis</i> - 4d , Ar = <i>p</i> -MeC ₆ H ₄ 50% y, 91% ee <i>cis</i> - 4e , Ar = <i>p</i> -ClC ₆ H ₄ 46% y, 92% ee	 <i>trans</i> - 4c , Ar = Ph 44% y, 98% ee <i>trans</i> - 4d , Ar = <i>p</i> -MeC ₆ H ₄ 48% y, 98% ee <i>trans</i> - 4e , Ar = <i>p</i> -ClC ₆ H ₄ 44% y, 98% ee	 <i>cis</i> - 4f 49% y, 95% ee <i>trans</i> - 4f 47% y, 99% ee
 <i>cis</i> - 4g 50% y, 97% ee <i>trans</i> - 4g 49% y, 93% ee	 <i>cis</i> - 4h 47% y, 98% ee <i>trans</i> - 4h 49% y, 92% ee	 <i>cis</i> - 4i 56% y, 44% ee ^b 42% y, –70% ee ^c <i>trans</i> - 4i 29% y, 98% ee ^b 34% y, –97% ee ^c	 <i>cis</i> - 4j 61% y, 54% ee ^b 63% y, –24% ee ^c <i>trans</i> - 4j 39% y, 95% ee ^b 26% y, –98% ee ^c

^a Conditions B: **3a** (1.0–5.0 mmol), (*S*)-B-Me (10 mol%), $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (0.6 equiv.), THF, rt. ^b (*S*)-B-Me (20 mol%), $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (1.0 equiv.). ^c (–)-Ipc₂BCl (1.2 equiv.), THF, –20 °C. (–)-Ipc₂BCl = (–)-diisopinocampheylchloroborane.



Scheme 4 Optimization of intramolecular C–H silylation of benzocyclobutenol **1a**.



Table 3 Stereospecific C–H functionalization of benzocyclobutenols 2^a

 5a, 56% y, 95% ee 98% es	 5b, R' = Me 68% y, 95% ee, >99% es 5c, R' = Cl 62% y, 88% ee, >99% es 5d, R' = F 40% y, 85% ee, 96% es	 5e, R = OMe 52% y, 93% ee, 99% es 5f, R = Me 59% y, 98% ee, >99% es 5g, R = NO2, 0% y 5h, R = N(CH2)4 30% y, 88% ee, 99% es
 5i, 78% y, 99% ee >99% es	 5j, R = Me 77% y, 99% ee, >99% es 5k, R = OMe 82% y, 99% ee, >99% es	 5l, R = Me 78% y, 99% ee, >99% es 5l', R = Me 84% y, 99% ee ^b , >99% es 5m, R = OMe 83% y, 99% ee, >99% es
 5n <div> <p>T 100 °C 57% y, 77% ee, 78% es</p> <p>T 80 °C 50% y, 83% ee, 84% es</p> <p>T 60 °C 49% y, 93% ee, 94% es</p> </div>	 5e''	

^a Conditions C: i. **2a** (0.5 mmol), [Ir(COD)OMe]₂ (0.05 mol%), Et₂SiH₂ (1.2 equiv.), THF, 30 °C; ii. [Ir(COD)Cl]₂ (2.5 mol%), Me₄Phen (6 mol%), **A** (1.0 equiv.), THF, 100 °C; iii. PhLi, THF, –78 °C; see the ESI for more details. ^b iii. KHCO₃ (2.5 equiv.), H₂O₂ (10 equiv.), THF/MeOH (1 : 1), 50 °C.

nucleophilic addition approach, treatment of the cyclization product with H₂O₂ provided diol **5l'** in 84% yield and 99% ee. Surprisingly, the reaction of substrate **2n** (99% ee) gave the product **5n** in only 77% ee. We assumed the partial racemization took place during the cyclization step, since acidic treatment of the hydroxysilylation product gave recovered alcohol **2n** in 99% ee. Gladly, we were able to improve the selectivity by lowering the reaction temperature (60 °C, 49% yield, 93% ee, 94% es).

Cyclobutanols were examined under optimal conditions as well (Table 4). Products **6a** and **6b** could be obtained in 27–48% yield. We assumed that the low yield of **6a** was due to the steric interaction of the phenyl and trialkylsilylhydroxy group, both were in a *cis* relationship. The reaction of 3-monosubstituted cyclobutanols **4b–4g** afforded the corresponding products *cis*-**6b–6g** and *trans*-**6b–6g** in good yields with the retention of ee. In the above cases, three contiguous chiral centers, even two quaternary centers were installed efficiently. The absolute configuration of *cis*-**6g'** was unambiguously determined by single-crystal X-ray diffraction analysis of its corresponding diol.²⁷ The diols *cis*-**6h'** and *trans*-**6h'** could be achieved upon treatment of cyclization products with H₂O₂ instead of

Table 4 Stereospecific C–H functionalization of cyclobutanols 4^a

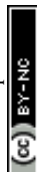
 6a, R = Ph 27% y, 92% ee, >99% es 6b, R = Me 47% y, 97% ee, >99% es	 <i>cis</i> - 6c , R = H 47% y, 92% ee, >99% es <i>cis</i> - 6d , R = Me 60% y, 93% ee, >99% es <i>cis</i> - 6e , R = Cl 61% y, 92% ee, >99% es	 <i>trans</i> - 6c , R = H 65% y, 98% ee, >99% es <i>trans</i> - 6d , R = Me 65% y, 97% ee, 99% es <i>trans</i> - 6e , R = Cl 71% y, 98% ee, >99% es
 <i>cis</i> - 6f 58% y, 94% ee, 99% es	 <i>cis</i> - 6g 28% y, 97% ee ^b , >99% es	 <i>cis</i> - 6g' ^c
 <i>trans</i> - 6f 54% y, 98% ee, 99% es	 <i>trans</i> - 6g 55% y, 94% ee ^b , >99% es	
 <i>cis</i> - 6h' 63% y, 97% ee ^c , 99% es	 <i>ent</i> - <i>cis</i> - 6i 77% y, 69% ee ^d , 99% es	 <i>cis</i> - 6j 69% y, 96% ee, 99% es
 <i>trans</i> - 6h' 56% y, 93% ee ^c , >99% es	 <i>ent</i> - <i>trans</i> - 6i 79% y, 98% ee ^c , >99% es	 <i>trans</i> - 6j 66% y, 92% ee, 97% es

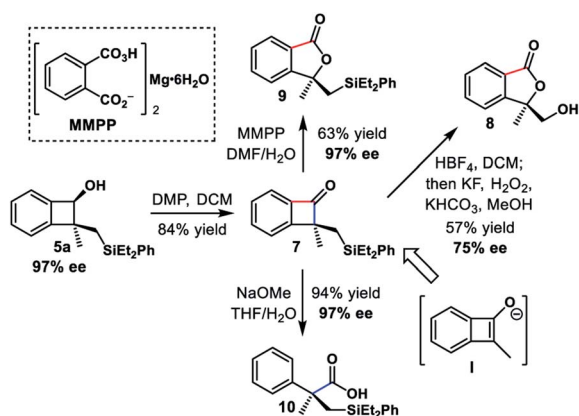
^a Reaction conditions: **4** (0.5 mmol), Ru(PPh₃)₃Cl (0.2 mol%), Et₂SiH₂ (1.5 equiv.), THF, 35 °C; ii. [Ir(COD)Cl]₂ (2.5 mol%), Me₄Phen (6 mol %), **A** (1.0 equiv.), THF, 100 °C; iii. PhLi, THF, –78 °C; see the ESI for more details. ^b ii. [Ir(COD)Cl]₂ (5 mol%), Me₄Phen (12 mol %). ^c iii. KHCO₃ (2.5 equiv.), KF (2.5 equiv.), H₂O₂ (10 equiv.), THF/MeOH (1 : 1), 50 °C. ^d *ent*-*cis*-**4i** (70% ee) was used. ^e *ent*-*trans*-**4i** (97% ee) was used.

phenyllithium. In addition, bicyclic substrates **4i**, **4j** smoothly furnished the corresponding enantioenriched products *cis*-**6i**, **6j** and *trans*-**6i**, **6j** with four contiguous carbon centers in good yields.

At this point, we conducted further transformations to explore the utilities of the chiral benzocyclobutene derivatives (Scheme 5). The oxidation of benzocyclobutenol **5a** afforded benzocyclobutenone **7** smoothly using Dess–Martin periodinane. This product could be viewed as the result of the alkylation of α -substituted benzocyclobutenone *via* elusive enolate intermediate **I**.

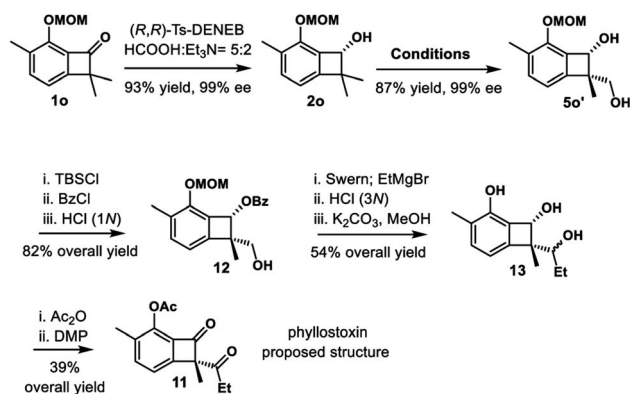
Subsequent Tamao–Fleming oxidation²⁹ with a concomitant cyclobutanone oxidation provided alcohol **8** in 57% yield, albeit with partial loss of enantiopurity. Furthermore, the regioselective Bayer–Villiger oxidation of **7** was achieved using MMPP,³⁰ giving phthalide **9** in 63% yield and 97% ee. Poor regioselectivity was observed when parent benzocyclobutenone was treated with a base.³¹ In contrast, exposure of **7** to sodium methoxide afforded phenylacetic acid derivative **10** as a single product in 94% yield and 97% ee *via* proximal bond cleavage.





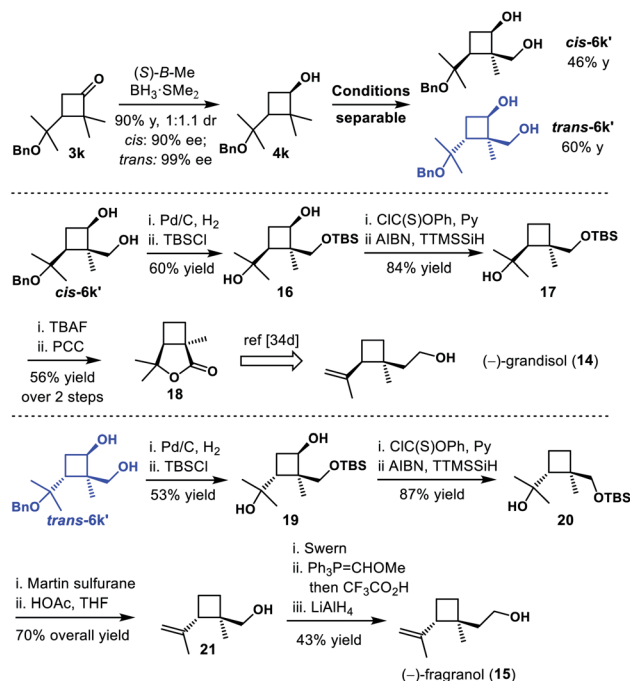
Scheme 5 Further transformations of benzocyclobutenol 5a.

Phyllostoxin (**11**) was isolated from fungal pathogen *Phyllosticta cirsii*, and it could represent a potential natural herbicide (Scheme 6).³² The structure was proposed to contain chiral α -quaternary benzocyclobutenone moiety. We envisioned that our strategy would provide a straightforward way to assemble the quaternary center of benzocyclobutenone, thereby confirming the proposed structure and determining the absolute configuration. Our synthesis commenced with enantioselective transfer hydrogenation of substrate **10**. Enantioenriched benzocyclobutenol **20** could be obtained in 93% yield and 99% ee using catalyst (*R,R*)-Ts-DENEB. Standard procedure, including hydrosilylation/C–H silylation/oxidation, provided diol **50'** in 89% overall yield and 99% ee. Various oxidation conditions were examined to oxidize diol **50'**, including Swern oxidation, Dess–Martin periodinane and PCC; unfortunately, the reaction only gave messy mixtures. Thus we turned to selective protection of the diol. Selective benzoylation could be achieved *via* three-step manipulation, giving primary alcohol **12** in 82% overall yield. Swern oxidation and nucleophilic addition of EtMgBr, followed by global deprotection, provided triol **13** in 54% yield over 3 steps. Of mention, benzoyl migration was observed in the EtMgBr addition step. Finally, selective

Scheme 6 Total synthesis of the proposed structure of phyllostoxin. Conditions: [Ir(COD)OMe]₂, Et₂SiH₂, THF, rt; ii. [Ir(COD)Cl]₂, Me₄Phen, A, THF, 100 °C; iii. KHCO₃, H₂O₂, THF/MeOH (1 : 1), 50 °C.

acylation of the phenol and subsequent oxidation furnished benzocyclobutenone **11** in 39% overall yield. However, the optical rotation and NMR spectral data did not match those reported for the natural product.

The monoterpene grandisol (**14**) was known as a main component of the sex pheromone of the cotton boll weevil, *Anthonomus grandis* Boheman, and other insects.^{33,34} The diastereomer fragranol (**15**) was isolated in many essential oil aerial parts of plant species such as *Achillea fragrantissima*, *A. falcata* and *Geranium tuberosum*.³³ Surprisingly, in comparison to grandisol, there is only one report on enantioselective synthesis of fragranol yet.³⁵ We postulated that our strategy would enable a divergent synthesis of these two diastereomers, starting from an optical resolution of cyclobutanone **3k** (Scheme 7). As expected, the CBS reduction of **1x** provided cyclobutanols *cis*-**4k** and *trans*-**4k** (90% yield, 1 : 1.1 dr, 90–99% ee). Subsequent C–H functionalization and oxidation gave diastereomers *cis*-**6k'** and *trans*-**6k'** in good yield. And both diastereomers could be easily separated by column chromatography. Debenzylation, selective silylation of the primary alcohol and Barton–McCombie deoxygenation provided cyclobutanes **17** and **20** uneventfully. Starting from cyclobutane **17**, deprotection and subsequent oxidation afforded lactone **18** in 56% overall yield, which led to formal total synthesis of (–)-grandisol **14**. Starting from cyclobutane **20**, regioselective dehydration with Martin sulfurane and removal of the TBS group furnished alkene **21** in 70% overall yield. Finally, (–)-fragranol **15** was obtained in three additional steps, which included oxidation to an aldehyde, olefination/hydrolysis and reduction.

Scheme 7 Divergent synthesis of grandisol and fragranol. Conditions: Ru(PPh₃)₃Cl, Et₂SiH₂, THF, 35 °C; ii. [Ir(COD)Cl]₂, Me₄Phen, A, THF, 100 °C; iii. KHCO₃, H₂O₂, THF/MeOH (1 : 1), 50 °C.

Conclusions

In conclusion, we developed a practical and robust approach to accessing enantioenriched cyclobutanols and benzocyclobutanols with all-carbon quaternary centers from readily available cyclobutanones and benzocyclobutenones. This strategy provided an alternative way to synthesize chiral α -quaternary cyclobutanones and benzocyclobutenones, which are otherwise directly inaccessible using enolate chemistry. Further transformations, including regioselective ring expansion and ring opening reactions were explored. This strategy was also applied to the synthesis of phyllostoxin (proposed structure), grandisol and fragranol. Finally, this sequential enantioselective reduction/C–H functionalization strategy could be utilized as a general method to synthesize α -quaternary cyclic carbonyl compounds, for example, 1-indanone, 2-indanone and cyclopentanone derivatives. These results will be reported in due course.

Data availability

Detailed condition optimization, experimental procedure, characterization data are available in the ESI.

Author contributions

J. C. designed the approach and performed the experiments, analyzed the experimental data and prepared the Supplementary Information. Z. S. and C. L. expanded the scope of the substrates. P. L. directed the investigations and prepared the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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