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Photoinduced Carboborative Ring Contraction Enables Regio- and Stereoselective Synthesis of Multiply Substituted Five-Membered Carbocycles and Heterocycles

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Abstract

We report herein a photoinduced carboborative ring contraction of monounsaturated six-membered carbocycles and heterocycles. The reaction produces substituted five-membered ring systems stereoselectively and on preparative scales. The products feature multiple stereocenters, including contiguous quaternary carbons. We show that the reaction can serve as a synthetic platform for ring system alteration of natural products. The reaction can also be used in natural product synthesis. A concise total synthesis of artalbic acid has been enabled by a sequence of photoinduced carboborative ring contraction, Rauhut-Currier reaction, and nitrilase-catalyzed hydrolysis. The synthetic utility of the reaction has been further demonstrated by converting the intermediate organoboranes to alcohols, amines and alkenes.

Ring contraction reactions are among the most useful strategic transformations for construction of complex carbocyclic and heterocyclic molecules. Favorskii, Wagner-Meerwein, pinacol and Wolff rearrangements, as well as ring contraction reactions mediated by hypervalent iodine and selenium reagents allow for efficient construction of densely substituted and less accessible smaller cyclic systems from the more abundant larger ones with predictable and high stereoselectivity.[1]

Six-membered ring is widely represented among secondary metabolites, e.g., terpenes and alkaloids. Cyclohexene motif can also be easily accessed by a number of regio- and enantioselective synthetic methods, e.g., the Diels-Alder cycloaddition.[2] The abundance and synthetic accessibility of the unsaturated six-membered ring system makes it an excellent precursor to the less readily accessible five-membered carbocycles and heterocycles.[3] In addition, structural alteration, including ring system modification, plays an important role in

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‡Author Contributions: These authors contributed equally

Supporting Information: The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures; characterization data (PDF)
Crystallographic data for **21** (CIF)
Crystallographic data for **31** (CIF)
Crystallographic data for **42** (CIF)

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medicinal chemistry of natural products, since it can lead to improved activity, metabolic stability, and target specificity.[4]

Photochemical activation enables generation of chemical intermediates that are not accessible from the ground states, e.g., *E*-cyclohexenes,[5] and triplet aryl cations,[6] whose reactivity is distinctively different from the thermally-generated species.

Cyclohexenes undergo photosensitized isomerization to strained and highly reactive *E*-isomers that readily participate in a variety of reactions, e.g., additions of alcohols and cycloadditions.[7] Experimental and computational evidence indicates that the more stable chair conformation is responsible for the reactivity observed for *E*-cyclohexene.[8,9] Despite the high angular strain within the ring, the reactions of *E*-cyclohexenes *E*-**1** can be remarkably stereoselective.[7,8]

We report herein an efficient photoinduced carboborative ring contraction that enables a regioselective synthesis of multiply substituted cyclopentanes **2** (Scheme 1). The reaction proceeds under mild conditions in the absence of additives and catalysts. In contrast to most other ring contraction processes, the photoinduced carboborative ring contraction results in an appendage of an additional side chain with a new stereocenter. The structure of the products **3** can be further diversified via conversion of the boryl group in the side chain to other functional groups. A number of secondary metabolites were readily converted to functionalized cyclopentanes with two new stereocenters, including quaternary all-carbon stereocenters.

Although earlier observations of the photoinduced reaction between cyclohexenes and trialkylboranes suggested that *syn*-carboboration with retention of the cyclohexane ring took place,[10] we observed a clean and efficient carboborative ring contraction (see additional discussion in SI) that, after oxidation, resulted in isolation of alcohol **4** as the sole product from the UV-induced (λ = 254 nm) reaction of 1-methylcyclohexene and triethylborane (Table 1). Further investigation showed that xylene isomers were superior to other aromatic hydrocarbons as photosensitizers, with *p*-xylene delivering a higher yield of alcohol **4** than *m*-, and *o*-xylenes (91% for *p*-xylene, 82% for *o*-xylene, and 71% for *m*-xylene). The reaction proceeded faster and with higher yields in more polar solvents, e.g., in alcohols, with ethanol as the optimal solvent. Other suitable solvents included dioxane, and tetrahydrofuran. The photochemical quantum yield for the formation of alcohol **4** was 0.26. The organoborane intermediate corresponding to product **4** was observed by means of NMR spectroscopy, indicating that the carboborative ring contraction is a photoinduced process that takes place before the oxidative work-up.

Interestingly, the reaction can also be carried out with a catalytic photosensitizer. Among photosensitizers evaluated,[11] ethyl benzoate (20 mol%) was found superior, delivering product **4** in 95% yield at 254 nm (in tetrahydrofuran) and 300 nm (in ethanol).

We next examined the scope of the reactants (Table 1). A number of boranes bearing primary and secondary alkyl groups were reacted with 1-methylcyclohexene under the optimal conditions.

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Trialkylboranes were readily prepared by hydroboration of alkenes with borane-tetrahydrofuran complex.[12] Alcohols **4-11** were obtained in good yields, including product **8** derived from tricyclopentylborane, and trialkylboranes that contain an aromatic group (**10**, **11**). Interestingly, 9-methoxy-9-borabicyclo[3.3.1]-nonane (9-BBN-OMe) also proved to be a suitable reacting partner, and the diol **12** was isolated after oxidation in 63% yield.

Other unsaturated six-membered carbocycles and heterocycles were studied as well. Cyclohexene produced the corresponding alcohols **13** and **14** in 98 and 90% yields, indicating that cyclohexenes with the unsubstituted C=C bond can also be used in the photoinduced carboborative rearrangement reaction. 1-*tert*-Butylcyclohexene also produced the sterically hindered alcohol **15** in 51% yield. Experiments with unsaturated six-membered oxygen and nitrogen heterocycles afforded tetrahydrofuran **16** and pyrrolidine **17**. While tetrahydrofuran **16** was isolated as a single diastereomer, the diastereomeric ratio was 10:1 for pyrrolidine **17**.

Terpenoids have important applications in medicine, agriculture, organic synthesis, as well as flavor and fragrance industries.[13] We were, therefore, interested in examining the generality of the photoinduced carboborative ring contraction reaction with several readily available terpenoids and their derivatives (Table 2). Terpinolene (**18**) produced the five-membered ring product **19** with >20:1 stereoselectivity. (*R,R*)-Carveol (**20**) afforded product **21** in a high yield and with 7–10 : 1 stereoselectivity. The minor diastereomer had the opposite configuration at the carbon atom of the alcohol stereocenter in the side chain. Alcohol **21** can be further purified by recrystallization to >20:1 d.r. The stereochemical assignment of the carveol product **21** was confirmed by X-ray crystallography. Similarly, TBS ether of carveol **22** afforded alcohols **23** and **24** in 63 and 58% yields, respectively. The syntheses of products **21** and **23** were readily carried out on gram scales. Interestingly, the all-carbon quaternary stereocenter in **21-24** was formed with very high stereoselectivity, as, in each case, the same configuration was observed for this stereocenter. Carvone-derived tertiary alcohol **25** gave rise to product **26** with two adjacent quaternary stereocenters in the newly-formed stereochemical triad indicating that carboborative ring contraction can be used for construction of molecules with contiguous quaternary stereocenters.[14] In addition, nerol oxide and valencene were readily converted to tetrahydrofuran **28** and 6/5-fused bicyclic alcohol **30** in 52 and 74% yields.

Steroids are functionally important biological molecules that play key roles in signal transduction and cell membrane function. Many steroids have found use in medicine and have been crucial in the development of drugs and in the elucidation of fundamental cellular processes.[13,15] Norsteroids are an important subclass of steroids.[16] We, therefore, proceeded to test the photoinduced carboborative ring contraction reaction in the synthesis of B-ring norsteroids. We found that a variety of naturally-occurring steroids and steroid derivatives were converted to the corresponding B-ring contraction products **31-45** (Table 3). The reactions proceeded with high regio- and stereoselectivity, presumably due to the rigidity of the steroidal structure, and the products were isolated as single diastereomers. Cholesterol and diosgenin produced the B-ring contraction products **31-36** with several trialkylboranes. B-Norsteroids from derivatives of pregnenolone (**37-39**), dehydroepiandrosterone (**40-42**),

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and azasteroids (**43-45**) were also prepared. Single crystal X-ray crystallographic analysis of the cholesterol-derived product **31** and the trifluoromethylated triol **42** confirmed the stereochemical assignment of the newly-formed stereocenters.

1-Methylcyclohexene reacted 1.9 times faster than cyclohexene. This result, in addition to the higher reaction rates in more polar solvents[6] may indicate that polar intermediates are involved in the photoinduced carboborative ring contraction process. Existing experimental evidence shows that the protonation of the C=C bond in *E*-cyclohexenes occurs stereoselectively from the outside face of the *E*-cyclohexene ring leading to an equatorial C–H bond in the resulting cyclohexyl cation.[8] The trialkylborane addition from the outside face of *E*-cyclohexene will result in dipolar intermediate **I** (Scheme 1).

The following migration of the endocyclic C3 atom to C1 can be accompanied by a migration of one of the alkyl groups R from boron to C2 position. Our experimental data indicate that the migration of the C3 atom to C1 results in the *trans*-configuration of the borylalkyl group (C2) with respect to the equato-rially oriented substituent at C4 in the rearrangement product **3**. A similar ring contraction step was proposed to explain the stereoselection in the terminal step of the Prins-pinacol rearrangement of allylic diol-derived acetals.[17] The migration of the alkyl group R from boron to C2 position can proceed with inversion or retention of the configuration at C2. Experimentally, the observed configuration at C2 in the major product **3** corresponds to the inversion pathway, while the minor product **3′** can be formed by the retention pathway.

Photoinduced carboborative ring contraction also enabled a concise total synthesis of artalbic acid (**46**)[18] (Scheme 2). The photoinduced reaction of (*S,S*)-carveol-derived TBS ether **47** with triethylborane was followed by conversion to unsaturated ketone **48** by a sequence of oxidations with trimethylamine *N*-oxide and Dess-Martin periodinane, α-selenylation, and hydrogen peroxide-induced selenoxide elimination.[19] 2-Cyanoethyl group was then appended to the α-position in enone **48** by means of a phosphinecatalyzed Rauhut-Currier reaction[20] with acrylonitrile as the only acrylic acid derivative that afforded the cross-Rauhut-Currier product. Nitrile **49** decomposed in strongly acidic and basic solutions at the higher temperatures that are typically required for the hydrolysis of nitriles to carboxylic acids. Two routes were, therefore, developed for this conversion. In the first one, nitrile **49** was hydrated to the primary amide with the aid of the Parkins catalyst **50**.[21] The primary amide was then converted to the corresponding *N,N*-bis-Boc-imide,[22] that was hydrolyzed to the acid at ambient temperature. Cleavage of the TBS group afforded artalbic acid (**46**). Alternatively, conversion of nitrile **49** to artalbic acid (**46**) was accomplished in two steps. In this route, desilylation of nitrile **49** was followed by a biocatalytic hydrolysis of the nitrile group to the carboxylic acid that was effected by nitrilase[23] at pH 7.2.

The C–B bond in organoboranes can be readily converted to a variety of functional groups.[12,24] For example, the photoinduced carboborative ring contraction of carveol **20** and its TBS ether **22** was followed by a reaction with 2-methyl-2-nitrosopropane dimer[25] resulting in the formation of *E*-alkenes **51** and **52** that were isolated as single isomers in 68 and 70% yields (Scheme 3). Cholesterol-derived B-norsteroid **53** with an *E*-alkenyl side chain was also prepared using the same procedure. Further, 4-alkoxyphenol **54** was readily

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prepared by a photoinduced carboborative ring contraction of 1-methylcyclohexene, followed by treatment with benzoquinone.

Interestingly, although formation of 2-alkylhydroquinones had previously been reported for a reaction of trialkylboranes with benzoquinone,[26] O-alkylation product **54** was isolated as a major product in this case, in line with the reactivity pattern previously observed for sterically hindered secondary *B*-alkylcatecholboranes.[27] In addition, amination[28] of the 1-methylcyclohexene-derived organoborane intermediate with hydroxylamine-*O*-sulfonic acid afforded amine **55**.

In conclusion, this paper describes a regio- and stereoselective photoinduced carboborative ring contraction. The operationally simple reaction produces substituted five-membered carbocycles and heterocycles on gram scales, and it can be used for structural modification of natural products containing a cy-clohexene ring and in natural product synthesis. The organoborane intermediates **3** can further serve as precursors to alcohols, amines, and *E*-alkenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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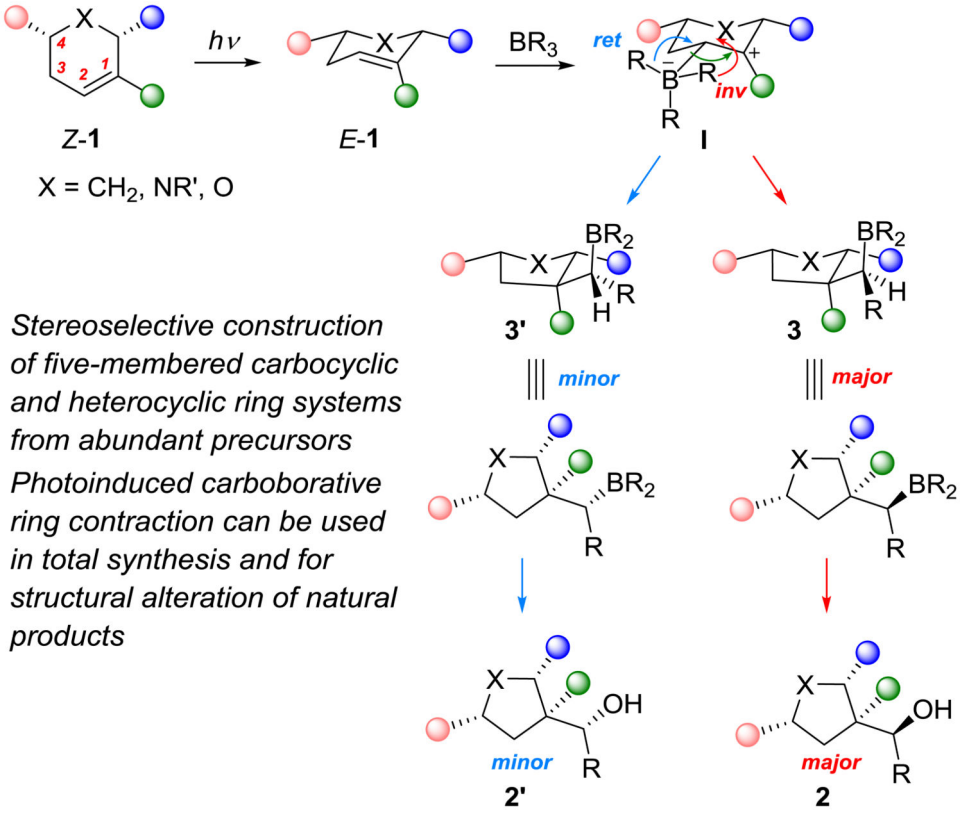

Scheme 1. Photoinduced Carboborative Ring Contraction

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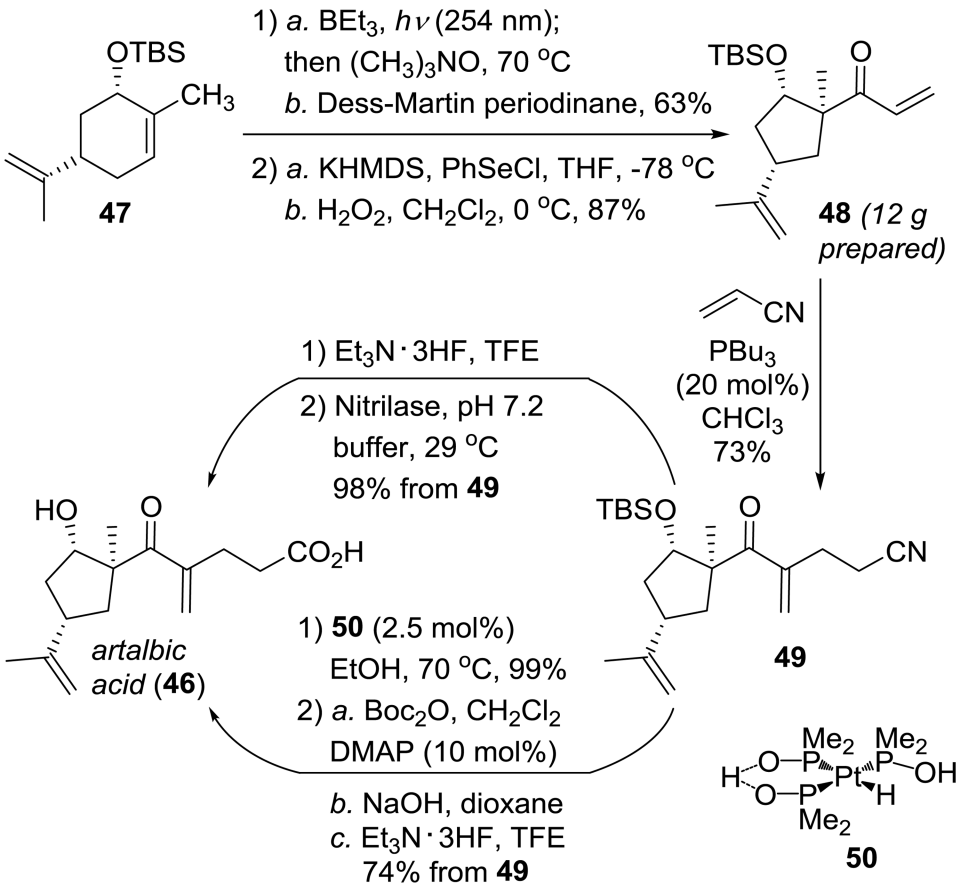

Scheme 2. Synthesis of Artalbic Acid

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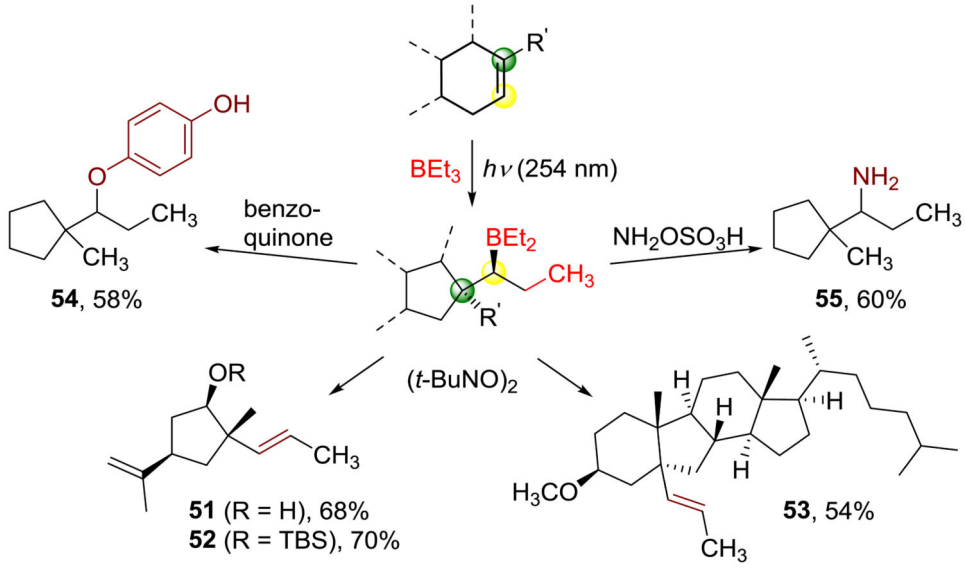

Scheme 3. Structural Diversification of the Carboborative Ring Contraction Products

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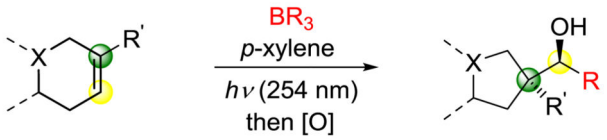
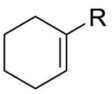
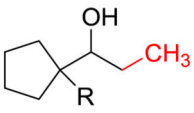
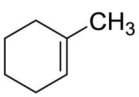
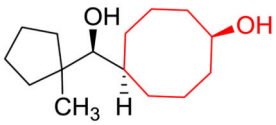
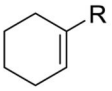
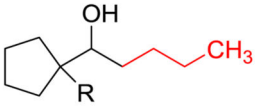
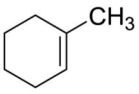
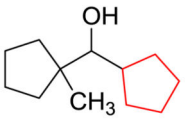
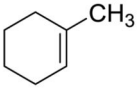
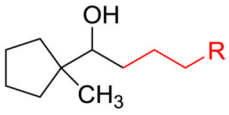
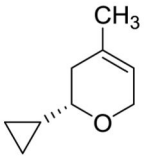
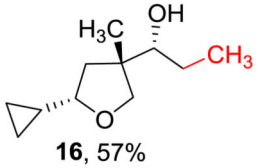
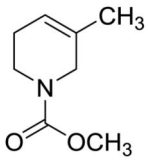
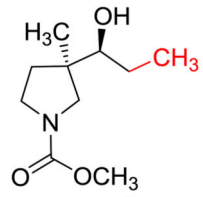
Table 1

Scope of the Photoinduced Carboborative Ring Contraction[a]



Precursor	Product, yield	Precursor	Product, yield
 R = H R = CH_3 R = *t*-Bu	 **13** (R = H), 98% **4** (R = CH_3), 91% **15** (R = *t*-Bu), 51%		 **12**, 63%
 R = H R = CH_3	 **14** (R = H), 90% **5** (R = CH_3), 91%		 **8**, 71%
	 **6** (R = Et), 73% **7** (R = *i*-Pr), 75% **9** (R = $CH(OEt)_2$), 61% **10** (R = Ph), 73% **11** (R = Bn), 61%		 **16**, 57%
			 **17**, 61%[b]

[a] Reaction conditions: cycloalkene (0.5–1 mmol), trialkylborane (1–1.5 mmol), EtOH (5 mL), *p*-xylene (2 mL), UV (254 nm), then H_2O_2, NaOH, or $Na_2CO_3 \cdot 1.5H_2O_2$.

[b] 10 : 1 d.r.

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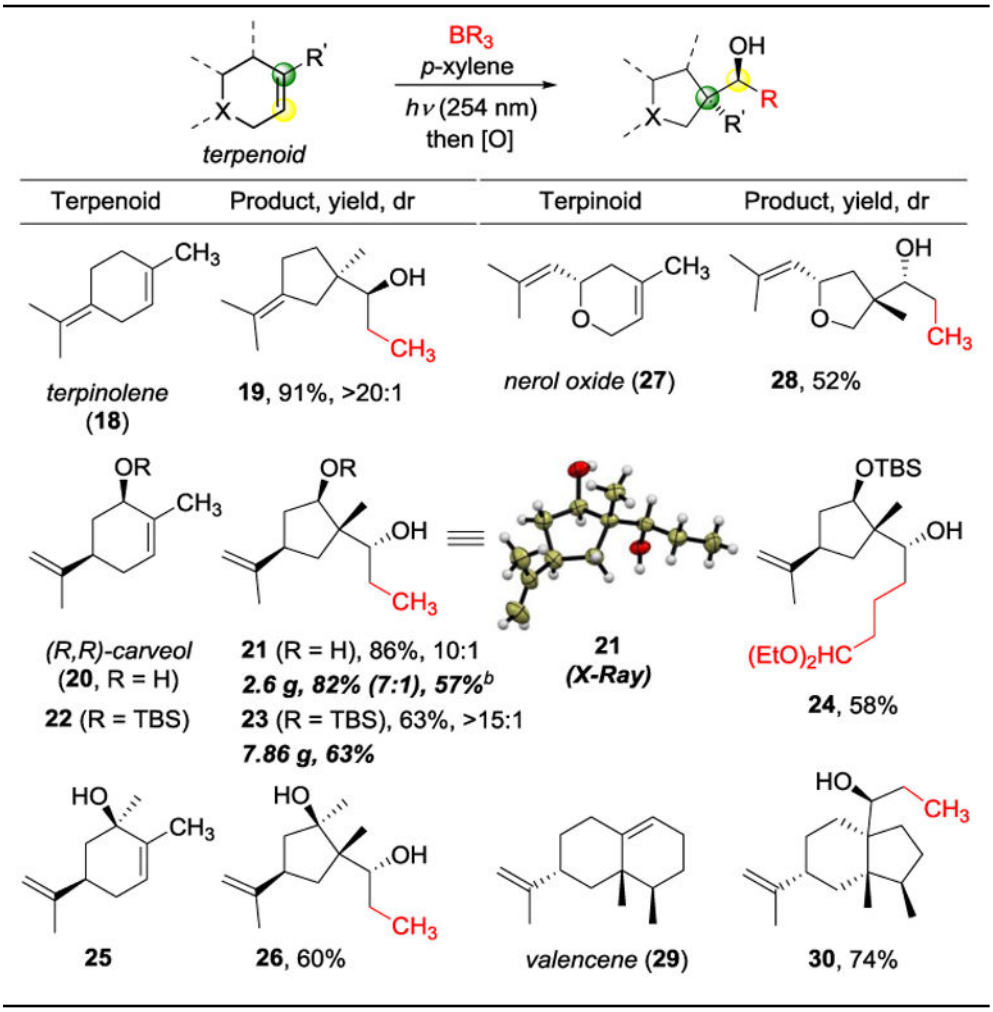
Table 2

Scope of the Photoinduced Carboborative Ring Contraction of Terpenoids[a]



[a]Reaction conditions: terpenoid (1 mmol), trialkylborane (1-1.5 mmol), EtOH (5 mL), *p*-xylene (2 mL), UV (254 nm), then H_2O_2, NaOH, or $Na_2CO_3 \cdot 1\,5H_2O_2$.

[b]Yield of pure diastereomer **21** after recrystallization. The minor diastereomer has the opposite configuration of the CH(OH) stereocenter in the side chain.

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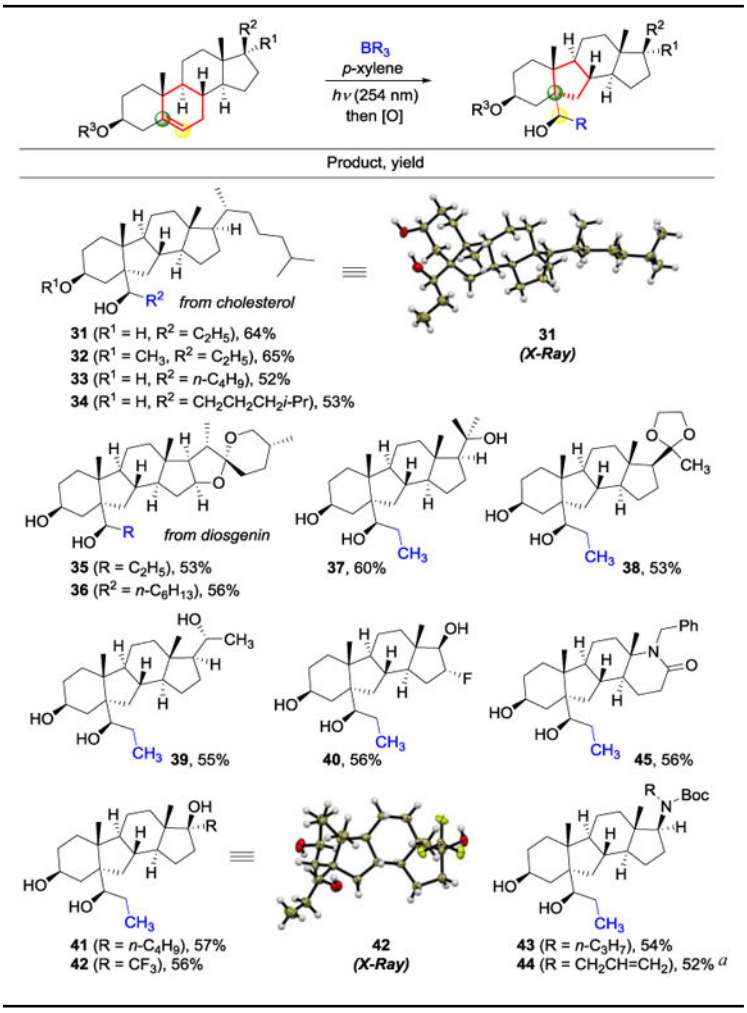
Table 3

Scope of the Photoinduced Carboborative Ring Contraction of Steroid Compounds[a]



Reaction conditions: steroid derivative (0.23–0.5 mmol), trialkylborane (0.3–0.6 mmol), EtOH or THF (2–4 mL), *p*-xylene (0.5–1 mL), UV (254 nm), then H_2O_2, NaOH.