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Regioselective Intermolecular [2 + 2]-Cycloaddition of α-Iodo-Unsaturated Ketones Promoted by Diisobutylaluminum Hydride

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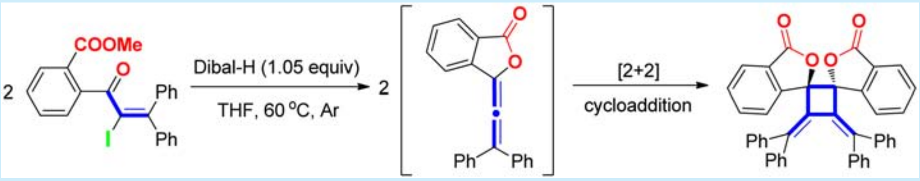
Supporting Information

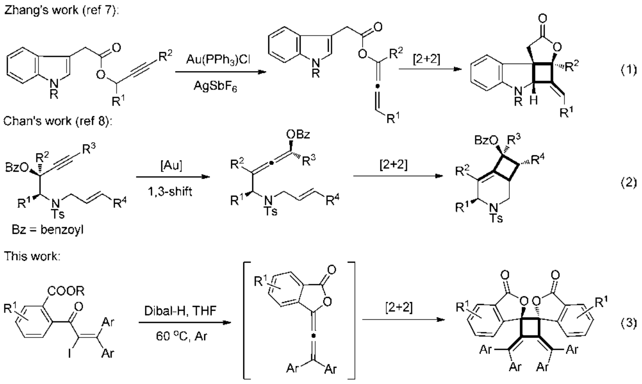


ABSTRACT: The development of intermolecular [2 + 2]-cycloaddition of α-iodo-unsaturated ketones in the presence of diisobutylaluminum hydride (Dibal-H) is reported to produce various trispirocyclic derivatives containing a cyclobutane ring. This sequential lactonization/[2 + 2]-cycloaddition proceeds in high regioselectivity under mild conditions.

Cyclobutane fragments were found in biologically important natural products and utilized as useful intermediates for the construction of more complex systems.[1] Therefore, the construction of cyclobutane subunits has continued to receive much attention. Compared with other strategies, the [2 + 2]-cycloaddition reactions stand out as more efficient methods for the preparation of such annulation systems with high atom economy.[2] To date, the [2+2]-cycloaddition of intramolecular or intermolecular alkenes has been extensively investigated photochemically and thermally.[3] Additionally, the [2 + 2]-cycloaddition reactions between alkenes and allenes have also been successfully developed to construct cyclobutanes with excellent efficiency.[4] Despite these advances, the selective [2 + 2]-cycloaddition of allenes for the production of the complex cyclobutanes has been explored limitedly.[5] Thus, the development of concise and efficient [2 + 2]-cycloaddition of allenes, including mild, commercially available reagents, and excellent selectivity, remain of practical significance.

Reportedly, allenes bearing an electron-donating group at the distal end would express stronger nucleophilicity and, consequently, be more likely to perform the [2 + 2]-cycloaddition reaction in a regio- and stereoselective manner.[6] Initially, Zhang developed a tandem cationic Au-catalyzed [2 + 2]-cycloadditions of allenylic esters in situ generated from propargylic esters with high efficiency and regioselectivity (Scheme 1, eq 1).[7] In 2011, Chan described the [2 + 2]-cycloaddition of 1,7-enyne benzoates to prepare functionalized 1-tosyl-1,2,3,6-tetrahydropyridine-fused cyclobutanes involving an activated allene intermediate (Scheme 1, eq 2).[8] Although these methods showed incomparable ingenuity and originality for the synthesis of cyclobutanes, the use of expensive Au(I) complexes as catalysts limited their wide applications in synthesis. α,β-Unsaturated ketones are versatile synthons that were smoothly synthesized by aldol condensation[9] or Meyer–Schuster rearrangement.[10] The C–C double bond carbons of α,β-unsaturated ketones have been extensively applied to [2 + 2]-cycloaddition reactions. However, the [2 + 2]-cycloaddition of α,β-unsaturated ketones involving carbonyl and α-position carbons has not been reported. To our knowledge, no successful examples of the [2 + 2]-cycloaddition of α-iodo unsaturated ketones promoted by commercially available Dibal-H have been presented. Herein, we reported an efficient Dibal-H-promoted lactonization/intermolecular [2 + 2]-cycloaddition of allenic esters generated in situ from 2-(2-iodo-3,3-diarylacryloyl)benzoates with excellent chemo- and regioselectivities under mild conditions (Scheme 1, eq 3).

Scheme 1. [2 + 2]-Cycloadditions of the in Situ Generated Allenylic Esters



Initially, the methyl 2-(2-iodo-3,3-diphenylacryloyl)benzoate (**1a**) was selected as the substrate to study the [2 + 2]-cycloaddition (Table 1). When **1a** was treated with 1.0 equiv of

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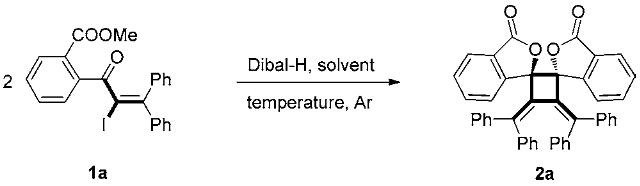
Table 1. Initial Evaluation of the [2 + 2]-Cycloaddition Reaction Conditions[a]



entry	Dibal-H (equiv)	solvent	temp (°C)	yield[b] (%)
1	1.0	THF	60	67
2	1.05	THF	60	73
3	1.1	THF	60	65
4	1.5	THF	60	63
5	1.05	toluene	60	27
6	1.05	$ClCH_2CH_2Cl$	60	33
7	1.05	1,4-dioxane	60	nr
8	1.05	THF	40	56
9	1.05	THF	80	58
10	1.05	THF	60	61[c]

[a] All reactions were run under the following conditions, unless otherwise indicated: substrate **1a** (0.2 mmol), Dibal-H (diisobutylaluminum hydride, 1 M in THF, 1.05 equiv), anhydrous solvent (2 mL) under argon atmosphere for 2 h. [b] Isolated yield based on **1a**. [c] For 4 h.

Dibal-H (1 M in THF) in dry THF at 60 °C, to our delight, the desired cycloaddition product **2a** was obtained in 67% yield (Table 1, entry 1). The structure of **2a** was unambiguously confirmed by X-ray crystallographic analysis and demonstrated that the adjacent lactone functions were anti oriented (Figure 1).[11] Increasing the amount of Dibal-H to 1.05 equiv produced **2a** in 73% yield (Table 1, entry 2). Next, by increasing the dosage of Dibal-H to 1.1 equiv and 1.5 equiv, the reactions did not give better results (Table 1, entries 3 and 4). The study of the influence of different reaction media showed that toluene and $ClCH_2CH_2Cl$ were less effective (Table 1, entries 5 and 6), whereas 1,4-dioxane proved to be ineffective (Table 1, entry 7). Additionally, no better result was obtained when the reaction temperature was varied (Table 1, entries 8 and 9). Prolonging the reaction time to 4 h decreased the yield to 61% (Table 1, entry 10). Finally, the optimum conditions identified in terms of practicality and efficiency are the following: the use of 1.05 equiv of Dibal-H in anhydrous THF at 60 °C for 2 h.

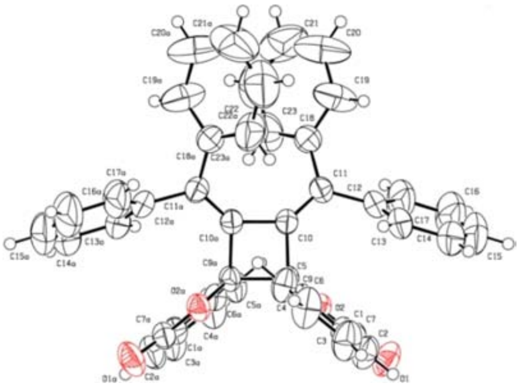
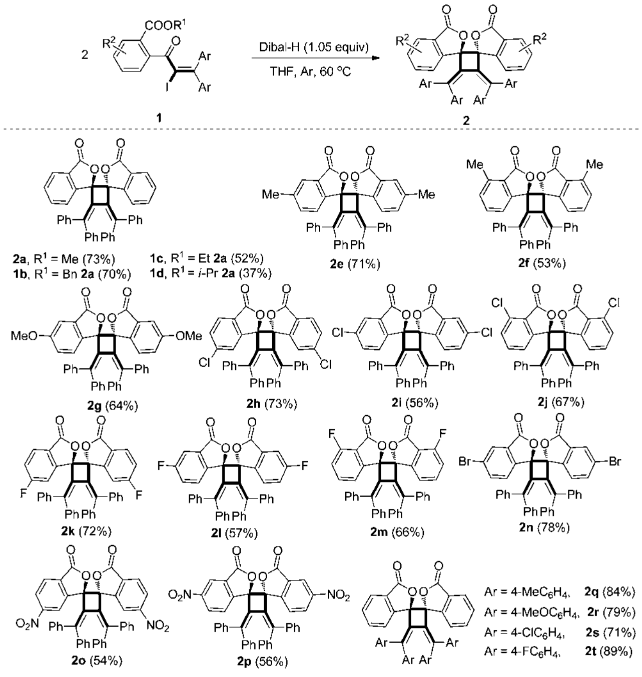


Figure 1. X-ray structure of **2a**.

Under the optimal conditions, various α-iodo-unsaturated ketones were synthesized to investigate the generality of the Dibal-H-mediated intermolecular [2 + 2]-cycloaddition, and the results are summarized in Scheme 2. This intermolecular dimerization showed high functional group tolerance and proved to be a concise methodology for the preparation of dimethylenecyclobutanes with excellent regioselectivities. First, the reactions of substrates **1b**–**d**, possessing benzyl, ethyl, and isopropyl substituents on R^1 were performed. Compounds **1b** and **1c** generated the desired product **2a** smoothly in moderate yields. However, the reaction of **1d** provided **2a** in low yield. Subsequently, we examined the electronic effects of the substituents on R^2 of the aromatic ring. Electron-donating substituents such as 5- or 6-methyl and 5-methoxy gave the corresponding products **2e**, **2f**, and **2g** in 71%, 53%, and 64% yield, respectively. Substrates **1h**–**n**, with a halo group on the aromatic ring, were also well tolerable under the standard conditions, producing the desired products **2h**–**n** in moderate yields. Variation in the position of the halo substituents from C-4 to C-5 on the aromatic ring decreased the yields of products (**2k** and **2l**). Moreover, electron-withdrawing groups, containing 4- or 5-nitro, were compatible in the cycloaddition, but their efficiency was unsatisfactory. Reactions with compounds **1q**, **1r**, **1s**, and **1t** bearing 4-methyl, 4-methoxy, 4-chloro, and 4-fluoro groups proceeded smoothly to furnish the corresponding adduct **2q**, **2r**, **2s**, and **2t** in good yields.

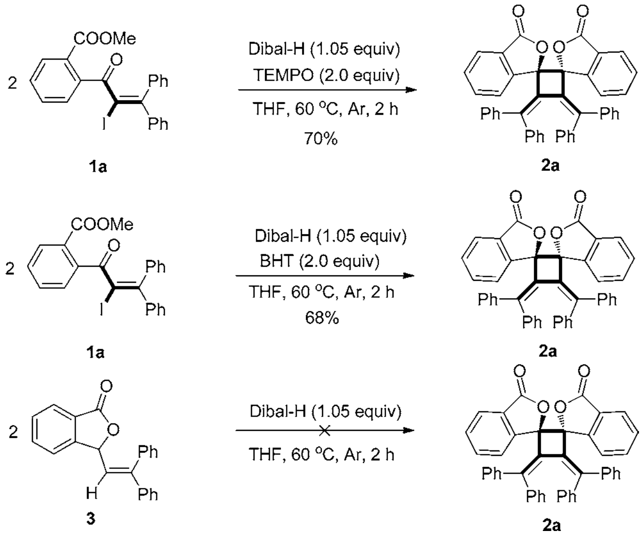
Scheme 2. Dibal-H-Promoted [2 + 2]-Cycloadditions for the Synthesis of Highly Substituted Dimethylenecyclobutanes 2[a]



[a] All reactions were run under the following conditions, unless otherwise indicated: 0.2 mmol of **1** with 1.05 equiv of Dibal-H in 2 mL of anhydrous THF under argon at 60 °C. Isolated yield based on **1**.

To further explore the mechanism of this intermolecular [2 + 2]-cycloaddition reaction, inhibition experiments were carried out (Scheme 3). When 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added, the [2 + 2]-cycloaddition reaction of **1a** was found to be uninhibited.[12] These results indicated that the [2 + 2]-cycloaddition of α-iodo-unsaturated ketones involves a collaborative process rather than a radical one. Furthermore, when 3-(2,2-diphenylvinyl)isobenzofuran-1-one (**3**) was sub-

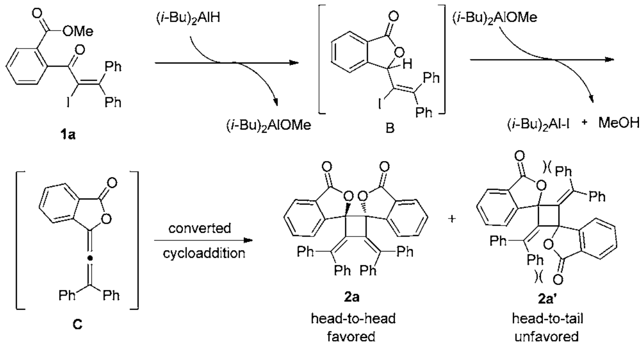
Scheme 3. Experiments for Mechanistic Studies



jected to the standard conditions, the desired product **2a** was not detected by thin-layer chromatography, which implied that this cycloaddition should not proceed through C−H activation.

According to the aforementioned observations, we propose a plausible mechanism outlined in Scheme 4 for this [2 + 2]-cycloaddition reaction. Initially, in the presence of diisobutylaluminum hydride ($(i\text{-Bu})_2AlH$), the reduction reaction of the carbonyl of α-iodo-unsaturated ketone **1a** is followed by lactonization to afford the alkenyl iodo intermediate **B** along with a diisobutylmethoxyaluminum ($(i\text{-Bu})_2AlOMe$). Subsequently, $(i\text{-Bu})_2AlOMe$ as base promotes the trans elimination of hydrogen with iodine groups on **B** to generate the allenylic ester intermediate **C**. Finally, the intermolecularly converted cycloaddition of **C** is achieved to form dimethylenecyclobutanes **2a** in a head-to-head manner. There are two plausible reasons to explain the obtained product regioselectivities: (1) the greater electron-donating ability of the lactone and (2) the steric hindrance between phenyl and lactone in a head-to-tail manner.

Scheme 4. Plausible Mechanism for the [2 + 2] Cycloaddition



In summary, we have developed a Dibal-H-promoted strategy for the highly selective construction of polysubstituted dimethylenecyclobutanes from readily available α-iodo-unsaturated ketones with high regioselectivity. This cycloaddition involves the cleavage of C−O and C−I bonds and the formation of two C−C bonds. Further mechanistic studies and applications of this Dibal-H-promoted lactonization/[2 + 2]-cycloaddition strategy are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02195.

Experimental procedures and compound characterization data (PDF)

X-ray data of **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) CCDC 1422313 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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