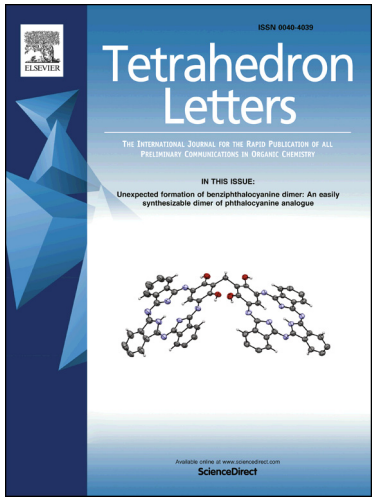

Synthesis of multi-substituted cyclobutenes: Cyclic strategy for [2+2] cycloadditon of ketene silyl acetals with propiolates

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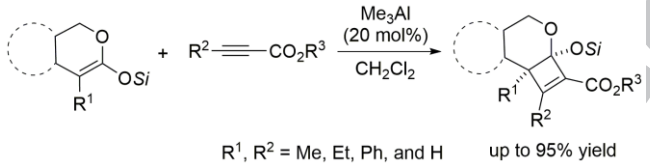

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Synthesis of multi-substituted cyclobutenes: Cyclic strategy for [2+2] cycloadditon of ketene silyl acetals with propiolates

Yousuke Yamaoka, * Motoki Ueda, Tohru Yamashita, Kazuma Shimoda, Ken-ichi Yamada, and Kiyosei Takasu*

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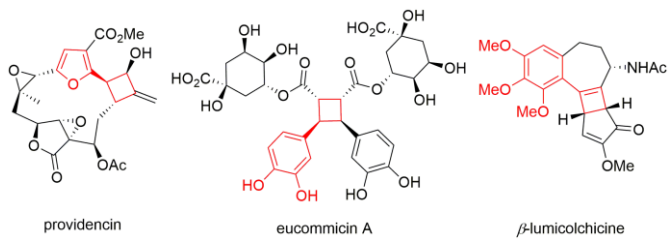
ABSTRACT

Cyclic ketene silyl acetals were utilized for [2+2] cycloaddition with propiolates to prevent an undesired electrocyclic ring opening reaction. Trimethylaluminum catalyzed this cycloaddition to afford the cyclobutene derivatives in high yields. The advantage of this reaction was highlighted by the successful application of *β*-substituted propiolates to afford the multi-substituted cyclobutenes. Furthermore, we applied this methodology to the late stage functionalization of natural product artemisinin.

Introduction

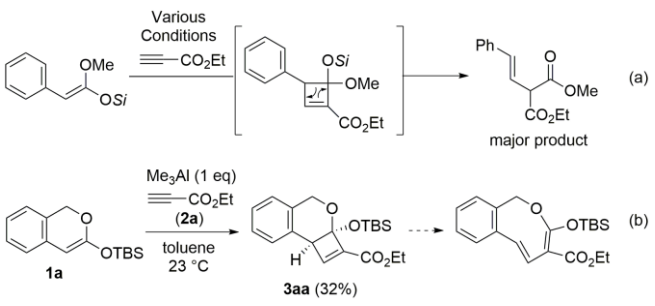
Four-membered carbocycles, such as cyclobutenes and cyclobutanes, have been utilized as synthetic intermediates, because of their ring strain.[1,2] In addition, they are sometimes found in bioactive natural products (Figure 1).[3] The simple route for functionalized cyclobutene derivatives is [2+2] cycloaddition of alkynes and alkenes, although the photoactivation is usually required.[4] We have recently developed a Brønsted acid-catalyzed [2+2] cycloadditon of silyl enol ethers with acrylates and propiolates to afford cyclobutane and cyclobutene derivatives, respectively.[5] This reactions can be carried out without the activation which is required special equipment.

Figure 1. Natural products containing a cyclobutane/cyclobutene scaffold.



Accordingly, we investigated [2+2] cycloaddition of ketene silyl acetals (KSA) with propiolates for the synthesis of highly functionalized and oxidized cyclobutene and cyclobutane for the purpose to synthesis these natural products above.[6,7] Although there are some reports of [2+2] cycloaddition of ketene silyl acetals with propiolates, to the best of our knowledge, [2+2] cycloaddition of α-aryl ketene silyl acetals has not been reported.[8]

Scheme 1. Preliminary results of synthesis of a cyclobutene bearing an aromatic ring.



At the outset of our study, [2+2] cycloaddition of KSA derived from methyl phenylacetate with ethyl propiolate was

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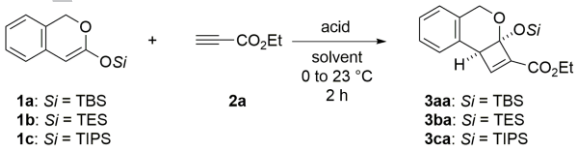
investigated (Scheme 1a). The reaction catalyzed by various Brønsted acids or Lewis acids failed to give the desired cyclobutene because of its thermal ring opening reaction. Bloomfield et al. reported that bicyclo[4.2.0]octene can undergo thermal ring opening at high temperature to give *cis,trans*-cyclooctadiene, but this compound could not be isolated because of a rapid reverse reaction to the starting material.[9] Thus, we hypothesized that the use of cyclic KSA from isochromanone would prevent the thermal ring opening reaction. As expected, [2+2] cycloaddtion of cyclic KSA **1a** from 3-isochromanone with ethyl propiolate (**2a**) promoted by an equimolar amount of trimethylaluminum afforded the desired cyclobutene **3aa** bearing an aromatic ring in 32% yield (Scheme 1b). Herein we wish to report [2+2] cycloaddtion of cyclic KSAs of 3-isochromanone with propiolates to afford the cyclobutene derivatives bearing an aromatic ring. Furthermore, we investigated the generality of [2+2] cycloaddtion with simple KSAs, and the late stage functionalization of a natural product[10] and further transformations of cyclobutene derivatives.

Results and Discussion

We first optimized reaction conditions for cycloaddition of isochromanone-derived KSA **1a** with ethyl propiolate (**2a**) (Table 1). We found that the chemical yield could be improved to 60%, when the temperature was gradually raised from 0 to 23 °C (entry 1). After screening several Lewis acids, trimethylaluminium was a best catalyst.[11] Then a series of solvents were examined, and dichloromethane was a suitable solvent for this reaction to improve the chemical yield (entries 1-3). Gratifyingly, a catalytic amount of trimethylaluminum (20 mol%) gave the desired product in almost the same yield (entry 4). The effects of silyl substituents on KSA were evaluated (entries 4-6). Finally, the use of triisopropylsilyl group (**1c**) as a protecting group gave the best result (89% yield). The amount of trimethylaluminum could be reduced to 10 mol%, although the yield was decreased to 54% (entry 7). When 2 mol% of triflic imide (Tf_2NH) was used instead of trimethylaluminum, higher catalyst turnover numbers were observed and the product was produced in 47% yield (entry 8). However, increasing the amount of the catalyst did not improve the chemical yield (entry 9). Thus, the optimized conditions entailed the use of 20 mol% of trimethylaluminum as a catalyst and triisopropylsilyl group as a protecting group in CH_2Cl_2 (entry 6).

Table 1. Optimization of reaction conditions.[a]



entry	*Si*	acid (mol%)	solvent	yield (%)[b]
1	TBS (**1a**)	Me_3Al (100)	toluene	60 (**3aa**)
2	TBS (**1a**)	Me_3Al (100)	CH_2Cl_2	73 (**3aa**)
3	TBS (**1a**)	Me_3Al (100)	THF	0 (**3aa**)
4	TBS (**1a**)	Me_3Al (20)	CH_2Cl_2	70 (**3aa**)
5	TES (**1b**)	Me_3Al (20)	CH_2Cl_2	0 (**3ba**)
6	TIPS (**1c**)	Me_3Al (20)	CH_2Cl_2	89 (**3ca**)
7	TIPS (**1c**)	Me_3Al (10)	CH_2Cl_2	54 (**3ca**)
8	TIPS (**1c**)	Tf_2NH (2)	CH_2Cl_2	47 (**3ca**)
9	TIPS (**1c**)	Tf_2NH (5)	CH_2Cl_2	40 (**3ca**)

[a] Condition: KSA **1** (0.55 mmol), **2a** (0.5 mmol) in solvent (0.25 M) at 0 to 23 °C. [b] isolated yield.

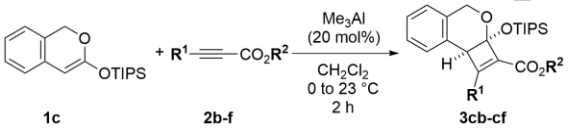


Table 2. Substrate scope of propiolates.[a]

entry	**2**	R^1	R^2	yield (%)[b]
1	**2b**	H	Me	74 (**3cb**)
2	**2c**	H	Ph	63 (**3cc**)
3	**2d**	Et	Et	81 (90)[c] (**3cd**)
4	**2e**	Ph	Et	67 (**3ce**)
5	**2f**	CO_2Et	Et	95 (**3cf**)

[a] Condition: KSA **1c** (0.55 mmol), **2** (0.5 mmol), and Me_3Al (20 mol%) in CH_2Cl_2 (0.25 M) at 0 to 23 °C. [b] isolated yield. [c] 18.5 mmol scale.

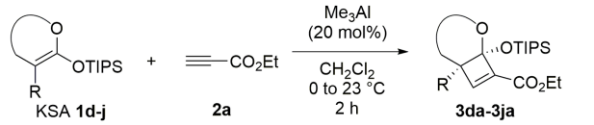
With the optimized conditions in hand, we turned to examine the substrate scope of propiolates with KSA **1c** (Table 2). Both alkyl (**2b**) and aryl (**2c**) esters of propiolic acid afforded the desired cyclobutenes in good yields (entries 1 and 2). Next, we investigated the [2+2] cycloaddition with propiolates bearing a β-substituent.[8b, 8e, 12] The reactions of **1c** with internal ynoates having an alkyl (**2d**) and an aromatic (**2e**) group gave the desired products (**3cd** and **3ce**) in good yields under the standard conditions, respectively (entries 3 and 4). A 6.2 gram scale synthesis was carried out to demonstrate the practical utility to afford the desired product **3cd** in 90% yield (7.7 g). The reaction with diethyl acetylenedicarboxylate (**2f**) also gave the desired product (**3cf**) in 95% yield (entry 5). Although we also conducted [2+2] cycloadditon with acrylate to give the cyclobutane as in the previous paper,[5c] the reaction of **1c** with ethyl acrylate led only to recover the starting material.

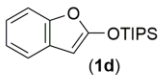
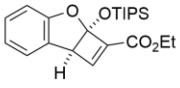
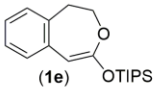
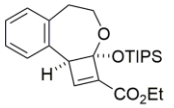
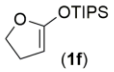
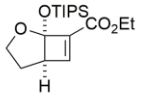
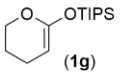
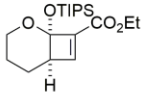
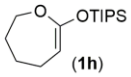
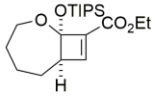
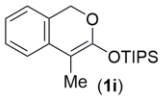
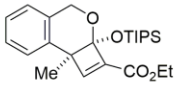
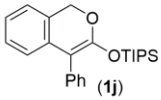
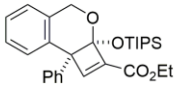
Next, substrate scope of various KSAs was examined (Table 3). KSA **1d** gave almost no desired product due to its less reactivity (entry 1). KSA **1e**, prepared from 4,5-dihydrobenzo[*d*]oxepin-2-one, gave **3ea** in 79% yield (entry 2). The [2+2] cycloaddition of monocyclic KSAs also worked well. 5-7 Membered KSAs reacted with ethyl propiolate to give the corresponding cyclobutenes (**3fa-3ha**) in moderate to good yields (entries 3-5). It is noteworthy that this methodlogy is superior to the previous reports, in term of chemical yields.[7c, 7d] Furthermore, KSAs bearing an alkyl or an aryl group at the α-position were applicable to this reaction to afford multi-substituted cyclobutenes (**3ia** and **3ja**) in high yields (entries 6 and 7).

The synthetic utility of the method was demonstrated by late stage construction of a cyclobutene ring onto a biologically active compound. Artemisinin is a peroxide-containing lactone isolated from the antimalarial plant *Artemisia annua*.[13] The low bioavailability and low aqueous solubility of artemisinin have prompted synthetic efforts to potent analogues compared to the parent molecule.[14] Thus, we investigated the late stage

functionalization of artemisinin using the developed methodology with its biologically crucial endoperoxide group retained. The [2+2] cycloaddition of ethyl propiolate with the lactone moiety proceeded without any problems to afford its analogue **4** in 95% yield in two steps (Scheme 2).

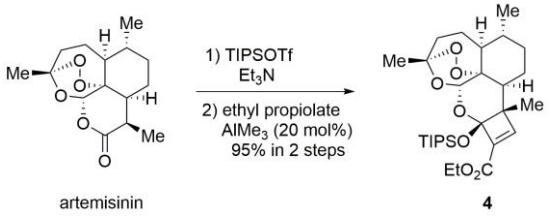
Table 3. Substrate scope of KSAs.[a]



entry	KSA	product	yield (%)[b]
1	 (**1d**)		trace (**3da**)
2	 (**1e**)		79% (**3ea**)
3	 (**1f**)		31% (**3fa**)
4	 (**1g**)		72% (**3ga**)
5	 (**1h**)		78% (**3ha**)
6	 (**1i**)		95% (**3ia**)
7	 (**1j**)		95% (**3ja**)

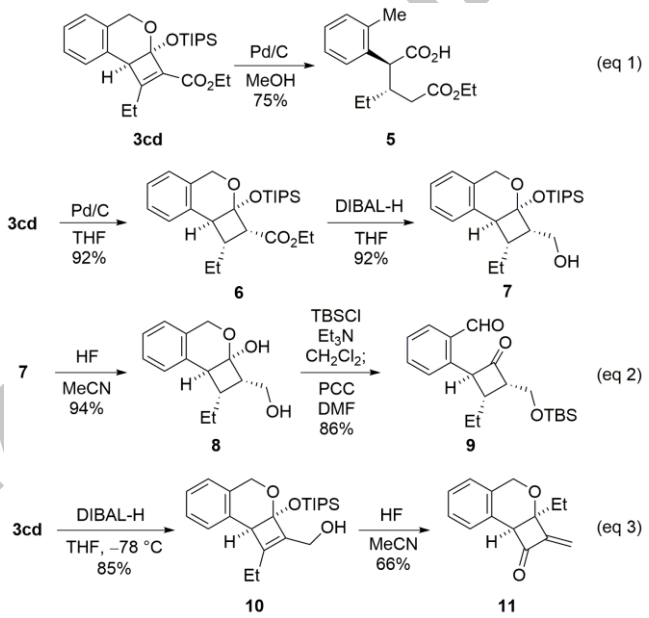
[a] Condition: KSA **1** (0.55 mmol), **2a** (0.5 mmol), and Me_3Al (20 mol%) in CH_2Cl_2 (0.25 M) at 0 to 23 °C. [b] isolated yield.

Scheme 2. Late stage installation of a cyclobutene moiety onto natural product artemisinin.



We explored further transformations of cyclobutene **3cd** (Scheme 3). Hydrogenation of cyclobutene **3cd** with palladium on carbon in MeOH under hydrogen atmosphere gave the undesired cyclobutene ring opened product **5** (eq 1). Gratifyingly, the solvent replacement of MeOH with THF prevented the side reaction and gave the desired product **6** in 92% yield as a single diastereomer. Interestingly, the hydrogenation occurred from the concave face, probably to avoid the bulky TIPS group. Reduction of the ester group and deprotection of the silyl group afforded the desired product **8**. The structure of **8** was unambiguously determined by X-ray crystallographic analysis. Finally, protection of the primary alcohol and PCC oxidation of the acetal moiety gave cyclobutanone **9** in high yield (eq 2). We observed an unique skeleton rearrangement of **10** under an acidic deprotection condition to gave the compound **11** in 66% yield (eq 3).

Scheme 3. Further transformations of cyclobutene **3cd**.



Conclusions

In conclusion, we have developed trimethylaluminum-catalyzed [2+2] cycloaddition of ketene silyl acetals with propiolates to provide several cyclobutene derivatives in high yield. Especially, we succeeded in the [2+2] cycloaddition of α-aryl ketene silyl acetals with propiolates by use of cylic ketene silyl acetals. Furthermore, we applied this methodology to the late stage functionalization of natural product artemisinin. The synthetic utility of the protocol was exemplified in a number of transformations to access multi-functionalized cyclobutenes and cyclobutanes. Further applications to the synthesis of the natural products are ongoing in our laboratory.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at .....

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11. The use of Et_2AlCl or $EtAlCl_2$ gave lower yield. The use of $Cu(OTf)_2$, $Zn(OTf)_2$, $Sc(OTf)_3$, or $Ga(OTf)_3$ were ineffective for this cycloaddition to give the hydration product of ketene silyl acetal.
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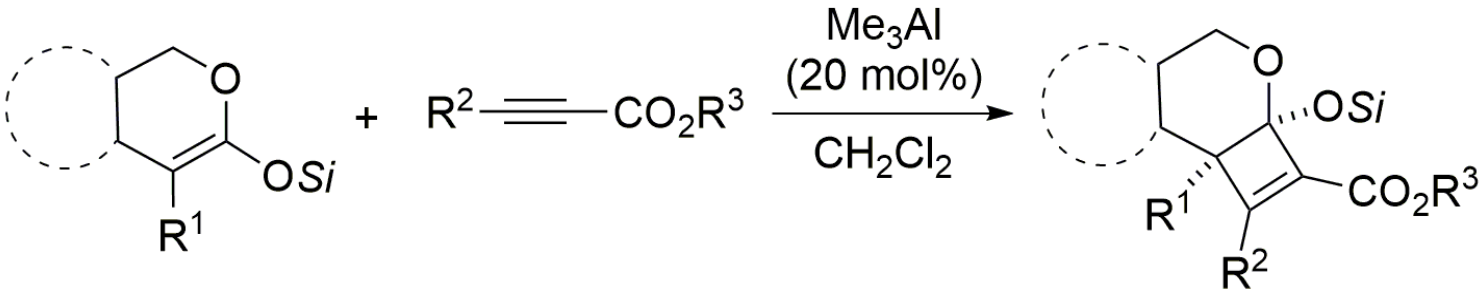
1, Cyclic ketene silyl acetals were utilized for [2+2] cycloaddition with propiolates.

2, Me_3Al catalyzed [2+2] cycloaddition afforded cyclobutenes in high yields.

3, Multi-substituted cyclobutenes could be synthesized.



R^1, R^2 = Me, Et, Ph, and H

up to 95% yield