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Communication

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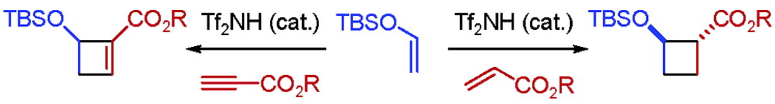

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COMMUNICATIONS

A Practical Catalytic Method for Preparing Highly Substituted Cyclobutanes and Cyclobutenes

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Four-membered carbocyclic ring systems are important structural units frequently present in biologically important compounds. In addition, cyclobutanes undergo facile and unique ring-opening and ring-expansion reactions, driven by the relief of ring strain. Therefore, four-membered ring compounds find use as key intermediates in synthetic routes to structurally complex targets. Despite the high preparative utility of cyclobutanes and cyclobutenes, only a limited number of practical and efficient methods exist for their synthesis.[1]

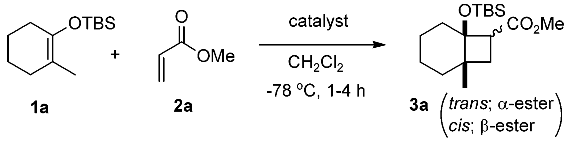
Recently, we reported that silyl enol ethers undergo hard Lewis acid (e.g., $EtAlCl_2$) catalyzed (2 + 2) cycloaddition reactions with α,β-unsaturated esters to produce substituted cyclobutanes.[2] These reactions are both highly efficient and highly regio- and stereoselective. However, substoichiometric amounts of the catalyst (ca. 20 mol %) are required even when perfectly anhydrous conditions are employed. In addition, the process is not applicable to substrates that contain Lewis acid sensitive functionality.

As part of continuing exploratory work, we have conducted studies aimed at expanding the applicability of this cycloaddition process. The results of this effort show that trifluoromethanesulfonimde (Tf_2NH) serves as an effective catalyst for (2 + 2) cycloaddition reactions of silyl enol ethers with α,β-unsaturated esters.

A survey of a number of reaction conditions led to the discovery that cyclobutane **3a** forming cycloaddition of silyl enol ether **1a** to acrylate **2a** is catalyzed by commercially available Tf_2NH (1.0 mol %) (Table 1, entry 1). The chemical yield and trans stereoselectivity of this process is higher than that observed in the analogous $EtAlCl_2$-promoted reaction (Table 1, entry 4).[2a] Even when 0.1 mol % of Tf_2NH is employed, reaction of **1a** and **2a** takes place at −78 °C (2 h) to give **3a** in a 98% yield (entry 2). The estimated turnover number for this reaction is 980. In contrast, a reaction using a stoichiometric amount of Tf_2NH results in low yielding of **3a** and decomposition of **1a** (Table 1, run 3). Also, TfOH does not promote the cycloaddition (entry 5).

To evaluate generality, Tf_2NH-catalyzed cycloaddition reactions of various substrates were examined (Table 2). Under the optimal conditions (1 mol % Tf_2NH, CH_2Cl_2, −78 °C), (2 + 2) cycloadditions of silyl enol ethers with acrylate **2a** take place to furnish the corresponding cyclobutanes **3b**−**f** in high yields and with high trans stereoselectivity (entries 1−5). It is noteworthy that 1 mol % Tf_2NH effectively promotes reactions of substituted acrylates, exemplified by the conversions of methacrylate **2b** and crotonate **2c** to highly substituted cyclobutanes **3g** and **3h**, respectively (entries 6 and 7). This contrasts with an earlier observation showing that stoichiometric quantities of $EtAlCl_2$ are required to catalyze cycloadditions of crotonate esters.

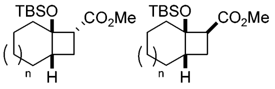
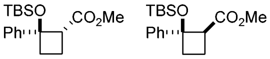
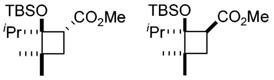
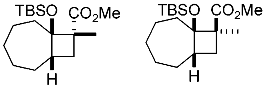
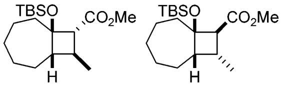
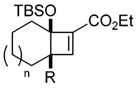
Table 1. Catalytic Activities for (2 + 2) Cycloaddition of **1a** with **2a**[a]



entry	catalyst (mol %)	% yield[b] (trans:cis)[c]
1	Tf_2NH (1.0)	92 (∼100 : trace)
2	Tf_2NH (0.1)	98 (∼100 : trace)
3	Tf_2NH (100)	trace
4[d]	$EtAlCl_2$ (20)	79 (95 : 5)
5	TfOH	0

[a] Reaction was performed using **1a** (1.1 equiv) and **2a** (1.0 equiv) in the presence of catalyst in CH_2Cl_2 at −78 °C. [b] Chemical yields were calculated based on **2a**. [c] Diastereomeric ratios were determined by ^1H NMR. [d] See ref 2a.

Table 2. Tf_2NH-Catalyzed (2 + 2) Cycloaddition Reactions[a]

entry	products		% yield[e] (ratio)
1[b]		**3b** (n = 0)	77 (>99 : ∼0)[f]
2[b]		**3c** (n = 1)	70 (80 : 20)[g]
3[b]		**3d** (n = 2)	91 (93 : 7)[g]
4[b]		**3e**	75 (72 : 28)[g]
5[b]		**3f**	93 (81 : 19)[g]
6[c]		**3g**	71 (87 : 13)[f]
7[c]		**3h**	75 (67 : 33)[f]
8[d]		**3i** (n = 0, R = H)	66 (–)
9[d]		**3j** (n = 1, R = Me)	53 (–)
10[d]		**3k** (n = 2, R = H)	80 (–)

[a] Reactions are performed using α,β-unsaturated esters (1 equiv), silyl enol ethers (1.1 equiv), and catalytic amounts of Tf_2NH in CH_2Cl_2 (0.1−0.3 M). [b] Tf_2NH (1.0 mol %), −78 °C, 2 h. [c] Tf_2NH (1.0 mol %), −20 to −40 °C, 3 h. [d] Tf_2NH (2.0 mol %), room temperature, 0.5 h. [e] Chemical yields were calculated based on α,β-unsaturated esters **2**. [f] Diastereomeric ratios were determined by isolated yield of each isomer. [g] Diastereomeric ratios were determined by ^1H NMR.

Reactions of silyl enol ethers with propiolate, catalyzed by Tf_2NH, were also examined.[3] Optimization studies revealed that cycloadditions of cyclic silyl enol ethers with ethyl propiolate (**2d**), promoted by 2 mol % Tf_2NH, occur at ambient temperature to generate cyclobutenes **3j**−**l** in good yields (entries 8−10).

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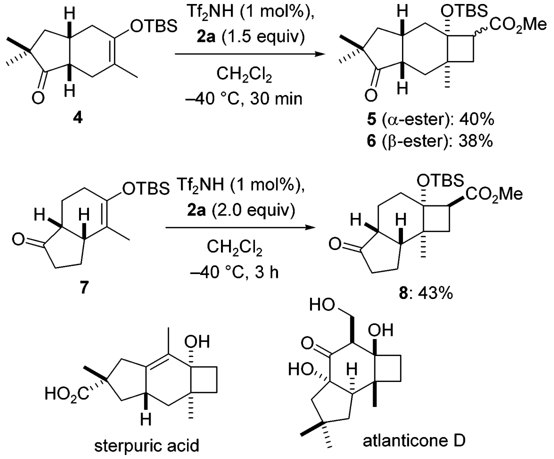
Scheme 1



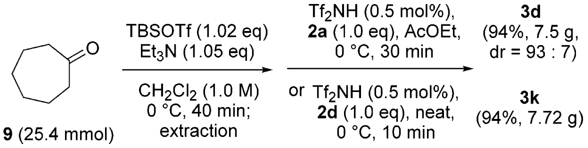
The methodology developed in this study is applicable to the construction of substances possessing terpenoid structures (Scheme 1). Reaction of silyl enol ether **4** with acrylate **2a** in the presence of Tf$_2$NH affords diastereomeric tricyclic adducts **5** and **6** in respective yields of 40 and 38%.[5] The adducts **5** and **6** possess the same relative configurations as members of the sterpurane natural product family (e.g., sterpuric acid).[4] Also, tricyclic cyclobutane **8**, which has the core structure of the protoilludanes (e.g., atlanticone D),[4] is obtained from a Tf$_2$NH-catalyzed reaction of silyl enol ether **7** with methyl acrylate. In contrast, only a trace amount of cycloadduct **8** is generated when EtAlCl$_2$ is used as a catalyst for this reaction. This result demonstrates that the organocatalyst Tf$_2$NH is compatible with substrates that contain Lewis basic keto carbonyl moieties.

Finally, exploratory studies aimed at further optimizing the cyclobutane-forming process show that the organic acid-catalyzed cycloaddition reaction can be successfully performed in various solvents, such as toluene, acetonitrile, dichloroethane, and ethyl acetate (see Supporting Information). The reactions of propiolate take place even under solvent-free conditions. Although reactions of acrylates normally require careful control of temperature below −40 °C, in ethyl acetate these cycloadditions take place at more conveniently accessed ambient temperatures.

In a further demonstration of the preparative potential of this chemistry, multigram quantities of four-membered carbocycles were obtained from cycloheptenone (**9**) in two steps, without purification of the intermediate silyl enol ether (Scheme 2). These two-step sequences, using methyl acrylate (**2a**) and ethyl propiolate (**2d**), lead to large-scale production (>7.5 g) of the respective bicyclic cyclobutane **3d** and cyclobutene **3k**, in excellent overall yields.

Yamamoto and co-workers reported earlier that Tf$_2$NH-catalyzed aldol reactions between TMS enol ethers and aldehydes[6] are promoted by highly reactive, in situ generated TMSNTf$_2$.[7,8] We also observed that a catalytic amount of pre-assembled TBSNTf$_2$ promoted the (2 + 2) cycloaddition reactions. Thus, Tf$_2$NH acts similarly as a precatalyst to produce the real catalyst TBSNTf$_2$ through reaction with the *tert*-butyldimethylsilyl enol ethers. It is consistent with the observation that the chemical yields for cyclobutane **3a** formation vary inversely with the amount of Tf$_2$NH (Table 1). Importantly, decomposition of TBSNTf$_2$ to form Tf$_2$NH during the course of these processes is reversed by reaction of the latter with the TBS enol ether substrates. As a result, high turnover numbers are achieved in this catalytic system.

Scheme 2



In summary, we observed that Tf$_2$NH serves as a highly efficient catalyst for (2 + 2) cycloaddition reactions of silyl enol ethers with acrylate and propiolate esters. The process is applicable to the stereoselective synthesis of highly substituted and structurally complex four-membered carbocyclic products. Studies designed to explore the full scope of this catalytic system for promoting cycloaddition reactions are currently being conducted.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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