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Cyclobutane ring formation by triflic imide catalyzed [2+2]-cycloaddition of allylsilanes

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Abstract—Cyclobutane forming [2+2]-cycloaddition reactions of allylsilane with electron-deficient olefin is promoted by triflic imide (Tf_2NH). Triflic imide is converted in situ to silyl triflic imide (R_3SiNTf_2), which serves as the actual catalyst for this process. When these reactions take place at higher than ambient temperatures, thermodynamically more stable *anti*-cyclobutanes are generated preferentially by equilibration of the initially formed adducts via retro [2+2]-cycloaddition.

As a consequence of the unique three-dimensional disposition of substituents and torsional ring strain driven high reactivity, cyclobutanes have received considerable attention by medicinal and synthetic chemists as drug-scaffolds and/or synthetic intermediates in routes targeted at medicinally useful substances.[1] It is widely accepted that [2+2]-cycloadditions are among the most efficient methodologies for construction of cyclobutane ring systems.[2] Although photochemical reactions have been widely studied in this context, their use is limited by difficulties in controlling chemo-, regio-, and stereoselectivities. Ground state [2+2]-cycloadditions are known to take place between electron-rich and highly electron-deficient olefin partners but these reactions require the use of a limited number of special substrates, such as vinyl sulfides, allenyl sulfides, and vinyl selenides.[1,2]

Recently, we reported that $EtAlCl_2$ catalyzes [2+2]-cycloadditions of readily available silyl enol ethers with α,β-unsaturated esters. The processes efficiently and selectively generate highly substituted cyclobutanes.[3] Further studies have shown that triflic imide (Tf_2NH)[4] promotes these [2+2]-cycloadditions and that silyl triflic imide (R_3SiNTf_2), generated from Tf_2NH and the silyl enol ether, serves as the actual catalyst (Fig. 1).[5] Although this reaction provides a convenient method to access cyclobutanes, it is restricted by the fact that the products contain siloxy substituents. Knölker and his co-workers reported that [2+2]-cycloadditions of allylsilanes with α,β-unsaturated esters yielding non-oxygenated cyclobutanes are promoted by stoichiometric amounts of $TiCl_4$.[6,7] To the best of our knowledge, there are no reports describing a catalytic version of this process.[8] We envisaged that Tf_2NH would serve to promote these types of allylsilane cycloaddition reactions.[9] Below, we describe the first examples of [2+2]-cycloadditions of allylsilanes with electron-deficient olefins that are catalyzed by Tf_2NH, and disclose information about the detailed mechanism of this process.

An initial exploratory study revealed that [2+2]-cycloaddition of allyltriisopropylsilane (**1a**) with methyl acrylate (**2**) in the presence of 5 mol % of Tf_2NH in

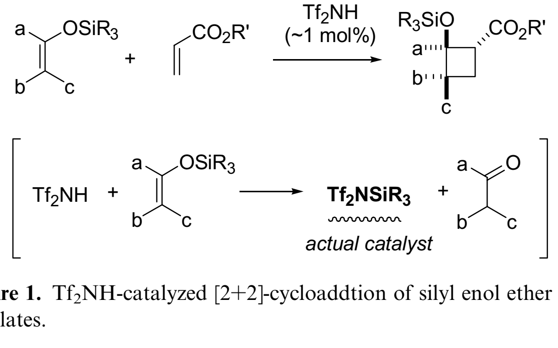

Figure 1. Tf_2NH-catalyzed [2+2]-cycloaddtion of silyl enol ether with acrylates.

Keywords: Cyclobutane; [2+2]-Cycloaddition; Allylsilane; Catalyst; Equilibrium; Triflic imide; Acrylonitrile.

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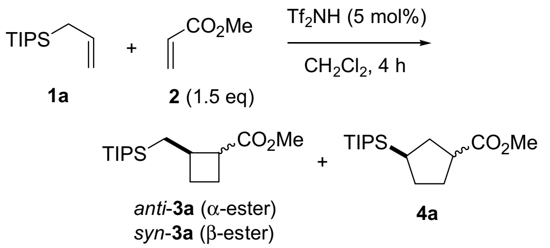
Table 1. Temperature effects on [2+2]-cycloaddition

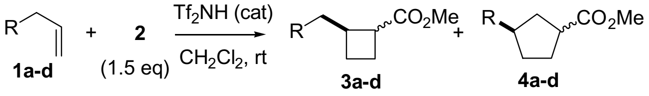


Entry	Temperature (°C)	% Yield (*anti*-**3a**:*syn*-**3a**:**4a**)[a]
1	−78	10 (50:50:0)
2	−40	50 (50:50:0)
3	0	83 (50:50:0)
4	25	86 (78:13:9)
5[b]	83	93 (54:5:41)

[a] Ratios were determined by ^{1}H NMR.

[b] Reaction was carried out in dichloroethane.

Table 2. Tf_2NH-catalyzed [2+2]-cycloadditions of **1**



Entry	**1** (R)	Catalyst (mol %)	Time (h)	% Yield (*anti*-**3**:*syn*-**3**:**4**)[a]
1	**1a** (^{i}Pr$_3$Si)	1	1	74 (57:39:4)
2	**1a**	1	24	91 (66:26:8)
3	**1a**	5	1	74 (69:23:8)
4	**1a**	10	1	74 (79:13:8)
5	**1b** (Me_3Si)	1	24	17 (55:45:0)
6	**1c** (^{t}BuMe$_2$Si)	1	24	82 (67:33:0)
7	**1d** (Ph_3Si)	1	24	49 (66:44:trace)
8[b]	**1a**	5	1.5	90 (70:30:trace)

[a] Ratios were determined by ^{1}H NMR.

[b] Ethyl acrylate was used instead of **2** to give **3e** (see Scheme 1).

CH_2Cl_2 occurs at −78 °C to yield silylmethylcyclobutane **3a** as a mixture of diastereomers (*anti*:*syn* = 1:1) in a 10% yield (Table 1, entry 1).[10] Reactions at −40 °C and 0 °C proceed smoothly to give **3a** in 55% and 83% yield, respectively (entries 2 and 3). Interestingly, although the reaction at ambient temperature (ca. 25 °C) produced **3a** in nearly the same yield as at 0 °C, a significantly different 6:1 *anti*/*syn* ratio of diastereomers was produced. Moreover, a small amount of cyclopentane **4a** was also formed (entry 4).[11] When the reaction is performed in refluxing dichloroethane, the *anti*-selectivity of the process increased to 11:1, the yield of **3a** decreased to 55%, and **4a** was generated in 38% yield (entry 5). The formation of cyclopentane and the temperature-dependency of the diastereomer ratio are consistent with observations made in studies of the $TiCl_4$ promoted reaction.[6a] *anti*-**3a**, *syn*-**3a**, and **4a** cannot be separated by SiO_2 column chromatography, but they are separable by HPLC. For the determination of the relative configurations, *anti*-**3a** and *syn*-**3a**[12] were individually converted into the respective *p*-bromobenzoates *anti*-**5a** and *syn*-**5a** by successive DIBALH-reduction and esterification (Fig. 2). NOESY experiments reveal that *syn*-**5a**, derived from minor isomer *syn*-**3a**, has a cis relationship between the triisopropylsilylmethyl and acyloxymethyl substituents.

Further investigations showed that the product ratio (*anti*-**3a**:*syn*-**3a**:**4a**) is also dependent on both reaction time and the amount of catalyst used (Table 2). For example, [2+2]-cycloaddition of **1a** takes place smoothly even in the presence of 1 mol % of the catalyst and the *anti* to *syn* ratio increases when long reaction times are employed (entries 1 and 2). When 10 mol % of Tf_2NH is used, *anti*-**3a** is selectively formed in a 1 h reaction (entry 4). The observed temperature, time, and catalyst loading dependencies indicate that the product ratios obtained ultimately in the [2+2]-cycloaddition process are a result of thermodynamic control. Good production of cyclobutanes was observed when allylsilanes having bulky alkylsilyl group, such as **1a** and **1c**, were used (entries 6–8).

Additional mechanistic insight was gained about the nature of the actual catalyst involved in the [2+2]-cycloaddition. Ghosez has shown that $TMSNTf_2$ is generated by reaction of allyltrimethylsilane and Tf_2NH at ambient temperature.[13] We observed that $TMSNTf_2$ (5 mol %), prepared according to the reported procedure and distilled prior to use,[13,14] promotes the cycloaddition reaction (Table 3). In addition, we found that only trace amounts of $TMSNTf_2$ are formed at −78 °C even when allyltrimethylsilane and Tf_2NH are mixed in the absence of solvent. This result explains why the cycloaddition reaction in the presence of Tf_2NH at −78 °C (Table 1, entry 1) is low yielding in contrast to the efficient reaction that takes place at this temperature when preformed $TMSNTf_2$ is used (Table 3, entry 1). The possibility that Tf_2NH serves as a Brønsted acid (H^+) catalyst is ruled out by the observation that the stronger Brønsted acid TfOH[15] does not promote cycloaddition. Based on these findings, we conclude that silyl triflic imide is the active catalyst for the cycloaddition process and suggest that it is continuously regenerated in the mixture by reaction of the allylsilane with the pre-catalyst Tf_2NH.[12] Consequently, the reaction proceeds smoothly even when the low catalyst loadings are used.

Table 3. [2+2]-Cycloaddition of **1a** with **2** in the presence of $TMSNTf_2$[a]

Entry	Temperature (°C)	Time (h)	% Yield (*anti*-**3a**:*syn*-**3a**:**4a**)[b]
1	−78	45	57 (52:48:0)
2	25	1	93 (75:8:17)

[a] Conditions: **1a** (1 equiv), **2** (1.5 equiv), $TMSNTf_2$ (5 mol %), CH_2Cl_2.

[b] Ratios were determined by ^{1}H NMR.

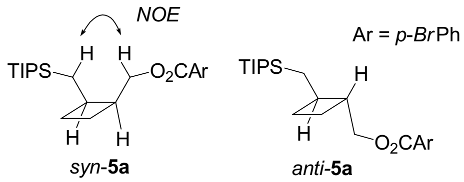


Figure 2. Structure of *syn*-**5a** and *anti*-**5a**.

Next, proof for the existence of thermodynamic control of the cycloaddition reaction was uncovered. Treatment of *anti*-**3a** with a mixture of Tf_2NH (5 mol %) and **1a** (5 mol %) in dichloroethane at reflux leads to the formation of a mixture of *anti*-**3a**, *syn*-**3a**, and **4a** in a ratio of 85:6:9 (Table 4, entry 1). Reaction of *syn*-**3a** under the same conditions affords a mixture of the three compounds in a respective ratio of 43:48:9 (entry 2). In contrast, **4a** was found to be stable when subjected to the same conditions. Moreover, conversion of **3a** to **4a** does not occur below 0 °C. We also observed that Tf_2NH itself promotes the retro [2+2]-cycloaddition process (Table 3, entries 3 and 4). Generation of $TIPSNTf_2$ from cyclobutane **3** and Tf_2NH in the retro reaction was clearly demonstrated by the results of the following crossover experiment. Both ^1H NMR and mass spectral analysis was used to show that treatment of ethyl ester **3e** (2.3:1 diastereomeric mixture) in the presence of excess methyl acrylate (**2**) and Tf_2NH (30 mol %) leads to formation of methyl ester **3a** (diastereomeric mixture) (Scheme 1). This observation indicates that allylsilane **1a** is produced in the retro reaction and that $TIPSNTf_2$ is subsequently generated by reaction of **1a** with Tf_2NH.

The mechanism proposed for the Tf_2NH-catalyzed [2+2]-cycloaddition reactions between allylsilanes and unsaturated esters is outlined in Figure 3.[6a] As depicted, silyl triflic imide is initially produced from allylsilane and Tf_2NH. This Lewis acid then promotes 1,4-addition of allylsilane **1** to acrylate **2** to give a zwitterionic intermediate. Intramolecular addition of the enolate anion in this intermediate to the β-silyl carbocation takes place to afford the cyclobutane product **3** (path a). This is a favorable pathway in reactions at temperatures lower than ca. 25 °C. On the other hand, at higher temperatures, a nonclassical pentavalent siliranium cation is competitively formed and it undergoes 5-*exo*-trig cyclizations to furnish cyclopentane **4** (path b).

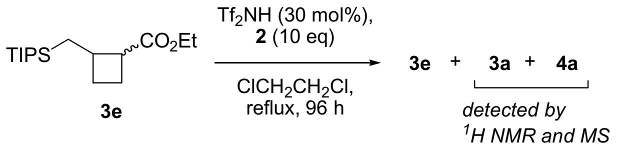
To test the generality of cyclobutane forming process, Tf_2NH promoted [2+2]-cycloadditions of **1a** with various α,β-unsaturated compounds were explored (Scheme 2). Reaction of excess (3 equiv) **1a** with methyl propiolate (**6**) proceeds to give cyclobutene **7** in 74% yield.[6b] Tf_2NH also promotes reaction of acrylonitrile (**8**) with **1a** at ambient temperature to give cyanocyclobutane **9** as a 1:1 mixture of diastereomers in 21% yield. Further optimization showed that nitrile **9** is obtained in 68% yield when reaction between **1a** and **8** is conducted at 150 °C in a sealed tube under solvent-free conditions. On the other hand, reactions with methyl vinyl ketone (**10**) and acrolein (**12**) at ambient temperature do not generate cyclobutane products but, rather, they afford the respective cyclopentanes **11** (47%, single diastereomer)[16] and **13** (14%, a mixture of diastereomers) via [2+3]-cycloaddition pathways. The exclusive formation of [2+3]-cycloadducts from enones is consistent with observations made in studies of the Ti-promoted reaction and seems to be a consequence of the differences between the stability of the α,β-unsaturated ester and

Table 4. Reaction of **3a** in the presence of catalyst

$$anti\text{-}\mathbf{3a} / syn\text{-}\mathbf{3a} \xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl, reflux}]{\text{Tf}_2\text{NH (cat)}} anti\text{-}\mathbf{3a} + syn\text{-}\mathbf{3a} + \mathbf{4a}$$

Entry	Substance	Catalyst (mol %)	% Yield (*anti*-**3a**:*syn*-**3a**:**4a**)[a]
1	*anti*-**3a**	Tf_2NH (5), **1a** (5)	83 (85:6:9)
2	*syn*-**3a**	Tf_2NH (5), **1a** (5)	78 (43:48:9)
3	*anti*-**3a**	Tf_2NH (10)	76 (87:3:10)
4	*syn*-**3a**	Tf_2NH (20)	54 (45:41:10)

[a] Ratios were determined by ^1H NMR.



Scheme 1.

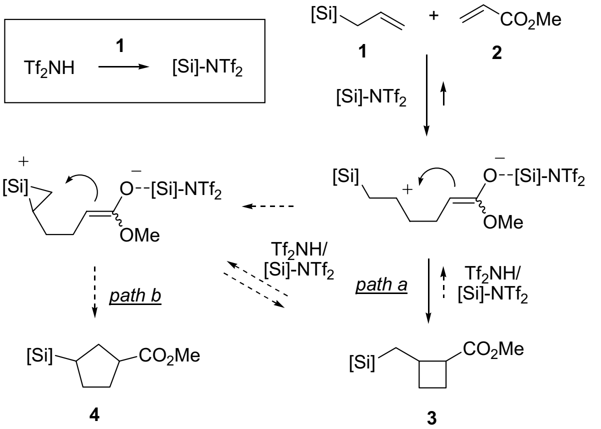
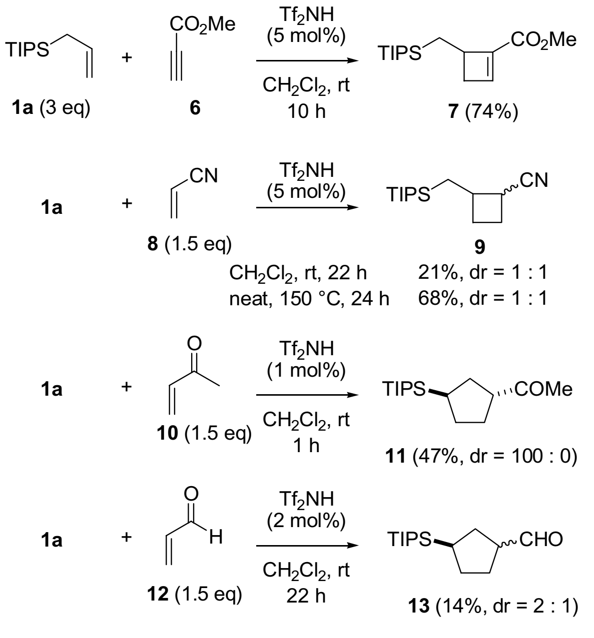


Figure 3. A proposed reaction mechanism (plain arrow: reaction would proceed even at below 25 °C; dashed arrow: reaction would proceed at more than 25 °C).



Scheme 2.

ketone enolate moieties present in the zwitterionic intermediates.

In summary, we have demonstrated that Tf_2NH-promoted [2+2]-cycloaddition reactions of allylsilane with acrylate, propiolate and acrylonitrile that take place efficiently to form substituted cyclobutanes. Silyl triflic imide, generated from the allysilane and Tf_2NH, serves as the active catalyst for these cycloaddition processes. Reactions at or below 0 °C lead to exclusive formation of cyclobutanes. At higher temperatures, an equilibrium is established in which the cyclobutane *anti*-**3** and cyclopentane **4** predominate. Finally, the process appears to proceed via the intermediacy of two zwitterionic species, one a classical β-silyl cation that affords the cyclobutane product and the other a siliranium cation that produces the cyclopentane product.

Acknowledgments

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10. Typical procedure for Tf_2NH-catalyzed [2+2]-cycloaddition: To a solution of **1a** (0.30 mmol) and **2** (0.45 mmol) in CH_2Cl_2 (2.0 mL) was added Tf_2NH (as 0.08 M toluene solution; 3 μM) at ambient temperature, and was stirred for 1 h. After addition of NEt_3 (15 μM) and concentration in vacuo, the resulting residue was chromatographed on silica gel (hexane/Et_2O = 20:1) to give a mixture of *anti*-**3a**, *syn*-**3a**, and **4a** in 74% yield (57:39:4). Each of the isomers was isolated by HPLC using a semi-preparative column (Mightsil Si 60 250–20). *anti*-**3a**: colorless oil; IR (neat) 2943, 2866, 1738, 1464, 1256, 1177 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.64 (s, 3H), 2.66–2.57 (m, 2H), 2.05–1.95 (m, 3H), 1.61–1.56 (m, 1H), 1.01–1.00 (m, 22H), 0.75 (dd, 1H, $J = 15.0$, 10.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 175.3, 51.3, 48.3, 37.2, 28.33, 21.18, 18.77, 17.35, 11.14; LRMS m/z 241 (M^+-43); Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34; found: C, 67.29; H, 11.08. *syn*-**3a**: colorless oil; IR (neat) 2943, 2866, 1738, 1468, 1362 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.18–3.14 (m, 1H), 2.87–2.83 (m, 1H), 2.72–2.18 (m, 1H), 2.13–2.07 (m, 1H), 1.98–1.94 (m, 1H), 1.93–1.87 (m, 1H), 1.01–0.98 (m, 21H), 0.71–0.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 51.1, 44.9, 34.8, 28.6, 20.0, 18.9, 18.8, 12.1, 11.3; LRMS m/z 241 (M^+-43); Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54 ; H, 11.34; found: C, 67.28; H, 11.01.
11. Compound **4a** was obtained as a mixture of inseparable diastereomers, and stereochemistry of each diastereomers was not determined.
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