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Construction of Highly-Functionalized Cyclopentanes from Silyl Enol Ethers and Activated Cyclopropanes by [3+2] Cycloaddition Catalyzed by Triflic Imide

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Abstract: [3+2] Cycloadditions of silyl enol ethers with donor-acceptor (D-A) cyclopropanes, such as 2-alkoxycyclopropanecarboxylates and 2-(*p*-methoxyphenyl)cyclopropyl phenyl ketone, proceed in the presence of a catalytic amount of triflic imide (Tf_2NH) to give functionalized cyclopentanes in high yield. The catalytic process allows promotion of the cycloaddition of substrates incorporating Lewis basic functions, such as ether and carbamate moieties. Moreover, multicomponent [4+2]-[3+2] cascade cycloadditions of α,β-unsaturated carbonyl compounds, 2-siloxydienes and D-A cyclopropanes to form highly-functionalized bicyclo[4.3.0]nonanes have been demonstrated.

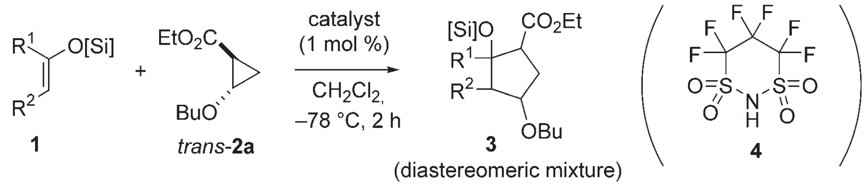
Keywords: cycloaddition; cyclopentanes; D-A cyclopropanes; multicomponent reactions; triflic imide; zwitterions

Cycloadditions are one of the most important reactions for the preparation of cyclic substances. In order to construct five-membered rings, several strategies, such as [3+2], [4+1], and [2+2+1] cycloadditions, are available. Among the methodologies, many efforts have been focused on [3+2] dipolar cycloadditions utilizing nitrones, azides, diazoalkanes to synthesize 5-membered heterocycles.[1] Donor-acceptor (D-A) substituted cyclopropanes[2,3] are utilized as equivalents of three carbon 1,3-dipole unit for the formation of 5-membered carbocyles. Kuwajima and his co-workers reported that [3+2] cycloadditions of D-A cyclopropanes, such as 2-alkoxy- and 2-phenylthiocyclopropyl carbonyl compounds, with silyl enol ethers were promoted by $SnCl_4$[4] and Me_2AlCl,[5] respectively, to furnish multi-functionalized cyclopentanes. Although several such [3+2] cycloadditions have been documented using various substances after their findings,[2,6,7] most of them require a stoichiometric amount of Lewis acid, except for a few exceptions.[4,8] As a part of our ongoing research program on catalytic [2+2] cycloaddition of silyl enol ethers to construct highly-substituted cyclobutanes,[9] we recently found that triflic imide (Tf_2NH)[10] efficiently catalyzes the [2+2] cycloaddition.[11] We have demonstrated that silyl triflic imide (R_3SiNTf_2),[12] which is generated *in situ* from Tf_2NH with silyl enol ethers, acts as the actual catalyst. We expected that Tf_2NH would be a new possibility for good catalysis of [3+2] cycloadditions of silyl enol ethers. We report herein [3+2] cycloadditions catalyzed by Tf_2NH, and its application toward a multi-component reaction, namely the [4+2]-[3+2] cascade cycloaddition, to afford the bicyclo[4.3.0]nonane framework.

At the outset of this study, the [3+2] cycloaddition of TBS enol ether (**1a**) with *trans*-ethyl 2-butoxycyclopropanecarboxylate (*trans*-**2a**)[4] as D-A cyclopropane was examined using several fluorinated Brønsted acid catalysts (Table 1, entries 1–4). Treatment of *trans*-**2a** with TBS enol ether **1a** in the presence of Tf_2NH (1 mol%) in CH_2Cl_2 at −78 °C for 2 h afforded the highly-substituted cyclopentane product **3a** in 69% yield as a mixture of four diastereomers (entry 1).[13] In contrast, the reaction using a stoichiometric amount of Tf_2NH resulted in only a trace yield of **3a** and decomposition of **1a** (entry 2). Imide **4**,[14] which is the cyclic analogue of Tf_2NH, also acts as a good catalyst (entry 4), whereas triflic acid (TfOH) does not promote the cycloaddition (entry 3).

As shown in Table 1 (entries 5–9), [3+2] cycloaddition of **1** with *trans*-**2a** proceeded smoothly by addition of a catalytic amount (1 mol%) of Tf_2NH to afford highly-functionalized cyclopentanes **3** in good yield. In contrast, the reaction of TMS enol ether **1b** afforded **3b** in 9% yield, along with desilylated product in 60% yield (entry 5). We have examined the

Table 1. [3+2] Cycloaddition of *trans*-ethyl 2-butoxycyclopropanecarboxylate) (*trans*-**2a**) with silyl enol ethers **1**.[a]



Entry	**1** (R^1, R^2, [Si])	Catalyst	Product	Yield [%][c]
1	**1a** (-$(CH_2)_4$-, TBS)	Tf_2NH	**3a**	69[d]
2	**1a**	Tf_2NH[b]	**3a**	trace
3	**1a**	TfOH	**3a**	0
4	**1a**	**4**	**3a**	65[d]
5	**1b** (-$(CH_2)_4$-, TMS)	Tf_2NH	**3b**	9[d,e]
6	**1c** (-$(CH_2)_4$-, TIPS)	Tf_2NH	**3c**	70[d]
7	**1d** (-$(CH_2)_4$-, TBDPS)	Tf_2NH	**3d**	73[f]
8	**1e** (-$(CH_2)_5$-, TBS)	Tf_2NH	**3e**	67[d]
9	**1f** (Ph, H, TBS)	Tf_2NH	**3f**	64[d]

[a] *Conditions:* **1** (1.2 equivs.), *trans*-**2a** (1 equiv.), catalyst (1.0 mol%), CH_2Cl_2 (0.1–0.2 M for *trans*-**2a**), –78 °C, 2 h.

[b] 100 mol% of catalyst was used.

[c] Isolated yields after SiO_2 column chromatography and/or GPC.

[d] Mixture of four diastereomers (detected by ^1H NMR).

[e] Desilylated product was obtained in 60% yield.

[f] Mixture of three diastereomers (detected by ^1H NMR).

possibility of [3+2] cycloaddition of **1a** with other cyclopropanes **2b–e** (Figure 1), however no reaction occurred under the same conditions. The results denote that both electron-donating and -withdrawing groups on cyclopropanes are necessary for promotion of the cycloaddition reaction.

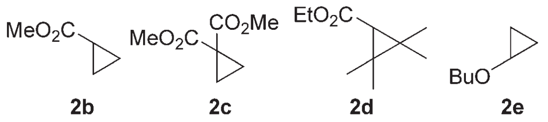


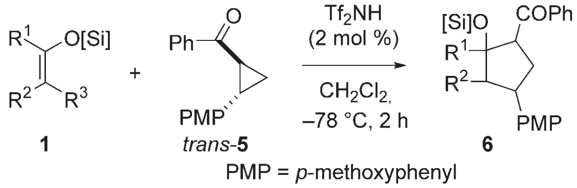
Figure 1. Cyclopropanes tested in our Tf_2NH-catalyzed [3+2] cycloaddition.

Next, we examined the [3+2] cycloaddition of silyl enol ethers **1** with *trans*-2-(*p*-methoxyphenyl)cyclopropyl phenyl ketone (*trans*-**5**)[15] as D-A cyclopropane. The *p*-methoxyphenyl group corresponds to a weaker electron-donating group, as opposed to the alkoxyl and alkylthio groups. As far as we know, there are limited examples for the [3+2] cycloaddition of D-A cyclopropanes possessing electron-donating aryl substituents.[16] Although the reactivity of **5** is lower than that of butoxycyclopropane **2a**, Tf_2NH (2–6 mol%) could promote the desired cycloaddition in a couple of hours to give multi-substituted cyclopentanes **6** in moderate to high yield (Table 2). The reaction of TBS enol ether **1a** with *trans*-**5** afforded the substituted cyclopentane **6a** in 84% yield as a mixture of four diastereomers (Table 2, entry 1),[13] whereas only two diastereomers of **6d** were obtained in the reaction of TBDPS enol ether **1d** under the similar conditions (entry 2).[5] Diastereomeric ratios are almost 1:1 in the reaction of cyclic TBDPS enol ethers **1d**, **g**, **h** with *trans*-**5** (entries 2–4), and the relative structures of both diastereomers **6h** have been determined by NOESY experiments (Figure 2). When the stereoisomeric cyclopropane *cis*-**5** was reacted with **1h** in the presence of Tf_2NH, the same product **6h** ($dr = 1{:}1$) was obtained in 84% yield (entry 5). On the other hand, acyclic TBDPS enol ether **1i** afforded **6i** as a 4:1 mixture of diastereomers (entry 6).

As a further synthetic demonstration, the construction of heterocyclic substances with Tf_2NH was examined (Scheme 1). Reaction of silyl enol ether **1j**, which was prepared from 4-tetrahydropyranone, with D-A cyclopropane *trans*-**5** in the presence of Tf_2NH afforded oxabicyclo[4.3.0]nonane **6j** as a mixture of four diastereomers in 71% yield. Silyl enol ether **1k**[17] containing a carbamate function also furnished azabicyclic compound **6k** in moderate yield. Moreover, the D-A cyclopropane-fused tetrahydropyran ring species **7**[18] promotes the [3+2] cycloaddition to furnish tricyclic compound **8** as a diastereomeric mixture. These results indicate that several Lewis basic functions in the substrate are compatible with Tf_2NH catalyst in the [3+2] cycloaddition.

We have further assessed multi-component reactions (MCR) involving a sequential Diels–Alder reaction and a [3+2] cycloaddition ([4+2]-[3+2] cascade

Table 2. [3+2] Cycloaddition of 2-(*p*-methoxyphenyl)cyclopropyl phenyl ketone (**5**) with silyl enol ethers **1**.[a]



Entry	**1** (R^1, R^2, R^3, [Si])	Product	Yield [%][e]
1	**1a** (-$(CH_2)_4$-, H, TBS)	**6a**	84[f]
2	**1d** (-$(CH_2)_4$-, H, TBDPS)	**6d**	80[g]
3[b]	**1g** (-$(CH_2)_3$-, H, TBDPS)	**6g**	74[g]
4[c]	**1h** (-$(CH_2)_4$-, Me, TBDPS)	**6h**	84[g]
5[d]	**1h** (-$(CH_2)_4$-, Me, TBDPS)	**6h**	94[g]
6[b]	**1i** (Ph, H, H, TBDPS)	**6i**	62[g]

[a] *Conditions:* **1** (1.2 equivs.), *trans*-**5** (1 equiv.), catalyst (2.0 mol%), CH_2Cl_2 (0.13 M for *trans*-**5**), −78 °C, 2 h.

[b] Reaction was conducted at −40 °C.

[c] 6 mol% of catalyst was used.

[d] *cis*-**5** was used instead of *trans*-**5**, and 4 mol% of catalyst was used.

[e] Isolated yields after SiO_2 column chromatography and/or GPC.

[f] Mixture of four diastereomers (detected by ^1H NMR).

[g] Mixture of two diastereomers (detected by ^1H NMR).

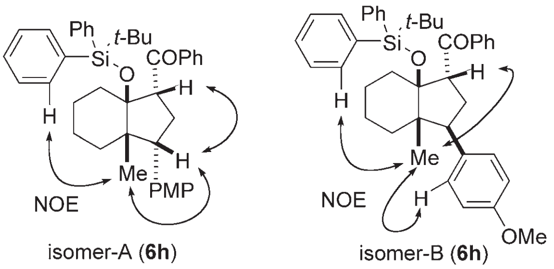
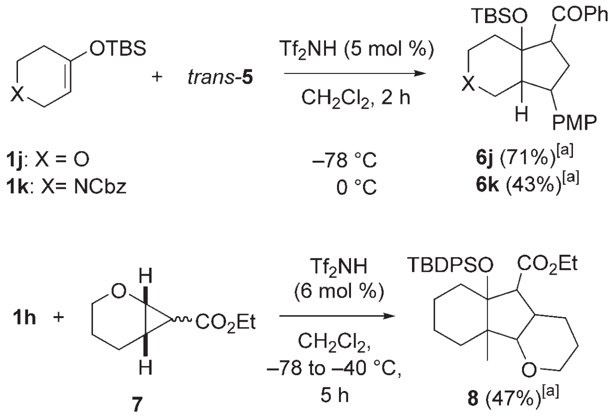


Figure 2. Selected NOEs of both diastereomers of **6h**.

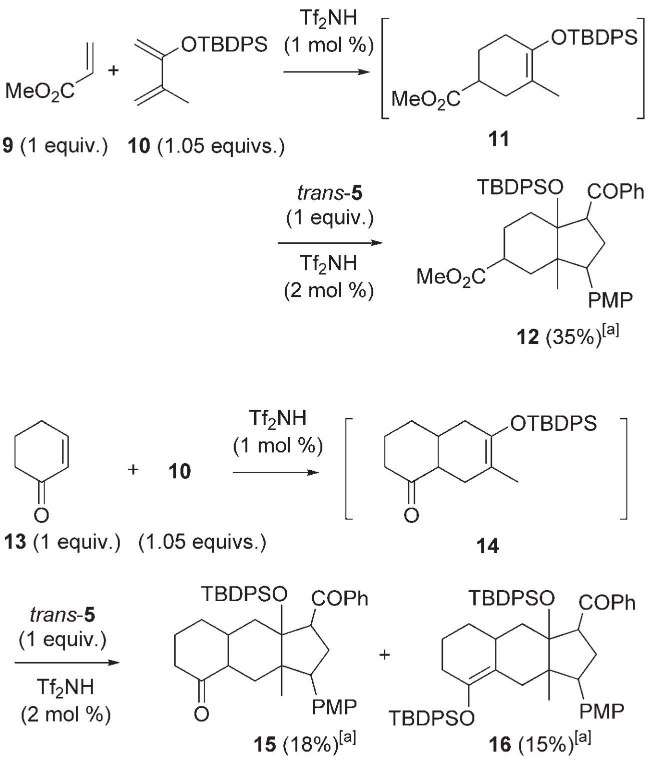


[a] As a mixture of several diastereomers.

Scheme 1.

cycloaddition) to assemble simple materials into polycyclic compounds.[19] When a mixture of acrylate **9**, 2-siloxydiene **10** and D-A cyclopropane *trans*-**5** was treated at once with Tf_2NH, the reaction resulted in the formation of a messy mixture. On the other hand, by sequential addition of the substrates as an alternative method, the desired MCR product **12** was obtained in moderate yield. Namely, Tf_2NH (1 mol%) was treated with a mixture of **9** and **10**, followed by addition of *trans*-**5** and additional Tf_2NH (2 mol%), to afford bicyclo[4.3.0]nonane **12** as a mixture of diastereomers (Scheme 2). The treatment of 2-cyclohexenone (**13**) with **10** and then with *trans*-**5** in the presence of Tf_2NH (1 + 2 mol%) afforded tricyclic compounds **15** and **16** in 18% and 15% yield, respectively, by means of sequential addition protocol.

A plausible mechanism of the catalytic [3+2] cycloaddition reaction is outlined in Figure 3. As mentioned above, silyl triflic imide (R_3SiNTf_2) is first produced from silyl enol ether and Tf_2NH. This Lewis acid then activates the D-A cyclopropane into a ring-opening 1,3-dipole, whose oxonium moiety is attacked by the nucleophilic enol silyl ether to form a zwitterionic intermediate. Then, intramolecular addition of the enolate anion in this intermediate to the oxonium cation takes place to afford the cyclopentane product. The speculation that not Tf_2NH but R_3SiNTf_2 serves as a real catalyst for the cycloaddition is consistent with the observation that the chemical yield of cyclopenetane **3a** varies inversely with the amount of Tf_2NH (Table 1, entries 1 and 2). The lack of stereospecificity observed in the reaction of both diastereo-



[a] As a mixture of several diastereomers.

Scheme 2.

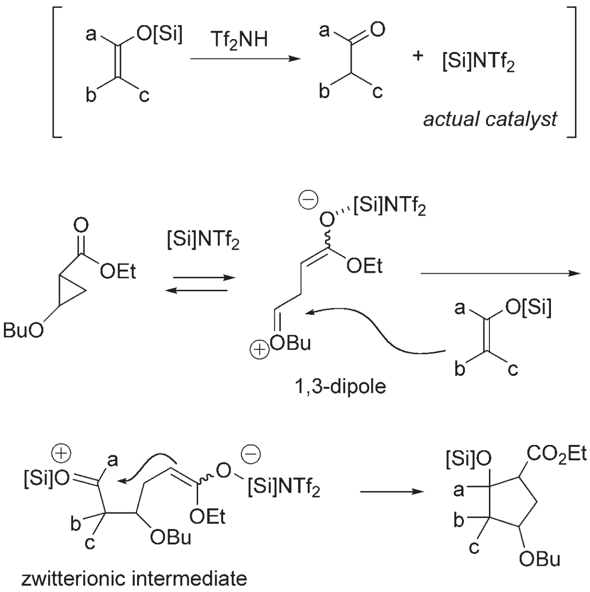


Figure 3. Plausible mechanism for Tf$_2$NH-catalyzed [3+2] cycloaddition.

mers *trans-* and *cis-***5** (Table 2, entries 4 and 5) suggests formation of a short-lived 1,3-dipole intermediate by ring-opening of the D-A cyclopropane.[4]

In summary, we observed that Tf$_2$NH serves as an efficient catalyst for [3+2] cycloaddition reactions of silyl enol ethers with D-A cyclopropanes to give highly-functionalized cyclopentanes in high yields. Tf$_2$NH catalyst enables the promotion of the [3+2] cycloaddition of substrates incorporating Lewis basic functions, such as ether and carabamate moieties, to give heterocyclic products. Moreover, we have demonstrated the multicomponent [4+2]-[3+2] cycloaddition of three different substrates, such as α,β-unsaturated carbonyl compounds, 2-siloxydiene and D-A cyclopropane, to give a highly-substituted bicyclo-[4.3.0]nonane skeleton in one pot. Further investigation is now ongoing to improve the stereoselectivity in the [3+2] cycloaddition and the chemical yields in the multicomponent reactions.

Experimental Section

General Procedure for [3+2] Cycloaddition

To a solution of *trans-***5** (1.0 equiv.) and silyl enol ether **1** (1.2 equivs.) in CH_2Cl_2 (0.13 M for *trans-***5**) Tf$_2$NH was added dropwise (2.0 mol%; 0.08 M toluene solution) at −78 °C. The reaction mixture was stirred at the same temperature for the appropriate time. The mixture was quenched with saturated aqueous $NaHCO_3$ solution, then diluted with Et_2O, and extracted with Et_2O three times. The combined organic layer was washed with brine, dried over Mg_2SO_4 and concentrated under vacuum. The residue was purified by GPC and/or SiO_2 column chromatography to give the desired cyclopentane **6**.

Typical Procedure for Multicomponent [4+2]-[3+2] Cycloaddition

To a solution of methyl acrylate (**9**; 18 μL, 0.20 mmol) and 2-siloxydiene **10** (67.4 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) Tf$_2$NH was added dropwise (0.08 M toluene solution; 25 μL, 2.0 μmol) at 0 °C. The reaction mixture was stirred at the same temperature for 35 min (TLC check). To the mixture D-A cyclopropane *trans-***5** (49.7 mg, 0.20 mmol) and Tf$_2$NH (0.08 M toluene solution; 50 μL, 4.0 μmol) were added at 0 °C, and stirred for 1 h at 0 °C and for an additional 1 h at ambient temperature. The mixture was quenched with saturated aqueous $NaHCO_3$ solution, then diluted with Et_2O, and extracted with Et_2O three times. The combined organic layer was washed with brine, dried over Mg_2SO_4, and concentrated under vacuum. The residue was purified with SiO_2 column chromatography and then GPC to give the desired **12** as a mixture of diastereomers; yield: 46.4 mg (35 %). The formation and purity of **12** was confirmed by elementary analysis.

Supporting information

Characterization data for new compounds are given in supporting information materials.

Acknowledgements

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