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Highly Effective Vinylogous Mukaiyama−Michael Reaction Catalyzed by Silyl Methide Species Generated from 1,1,3,3-Tetrakis(trifluoromethanesulfonyl)propane

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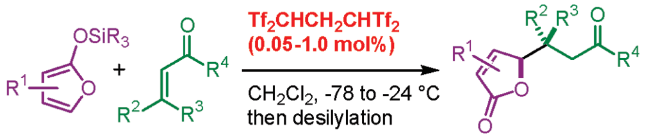

Significant low catalyst loading: up to 0.05 mol%
Stereoselective C-C bond formation between sterically hindered substrates

Silyl methide species in situ generated from 1,1,3,3-tetrakis(trifluoromethanesulfonyl)propane ($Tf_2CHCH_2CHTf_2$) performed as an excellent acid catalyst for the vinylogous Mukaiyama−Michael reaction of α,*β*-unsaturated ketones with 2-silyloxyfurans. Notably, the required loading of $Tf_2CHCH_2CHTf_2$ to obtain the 1,4-adducts in reasonable yield was significantly low (from 0.05 to 1.0 mol %). This carbon acid-mediated VMM reaction provides a powerful synthetic methodology to construct highly substituted *γ*-butenolide structure.

Introduction

Organic Brønsted acid such as carboxylic acid, phosphonic acid, and sulfonic acid is one of the most useful and popular catalysts in modern organic synthesis.[1] These organic acids are essentially green due to avoiding the use of metal salts, although the catalyst loading of Brønsted acids is generally higher than that of transition metal catalysts or Lewis acids. In addition, the low catalyst activity of organic catalysts severely limits their application to synthetic reactions.

As an alternative application of Brønsted acid to organic synthesis, in situ generation of silicon Lewis acids "R_3Si-A" by the reaction of Brønsted acids "H-A" with silylated nucleophiles "R_3Si-Nu" also attracts much attention.[2] This procedure has the following two advantages (Scheme 1): (1) simple operation without handling of easily hydrolyzed and fuming silicon Lewis acids[3] and (2) notably low catalyst loading of Brønsted acid through high catalyst activity[4] and "self-repairing" of generated silicon Lewis acids.[5,6] In addition, high activation of reaction substrates by catalytically active silicon Lewis acid would realize some bond formations between less reactive substrates such as sterically hindered substrates.

In general, it is known that the silylating activity (or Lewis acidity) of "R_3Si-A", which is possibly generated from Brønsted acid "H-A" with silylated nucleophiles "R_3Si-Nu", depends on both the leaving group ability of ligand

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(1) (a) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008. (b) *Asymmetric Organocatalysis*; Berkessel, A., Groeger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005; (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175.

(2) (a) Oishi, M. Silicon(IV) Lewis Acids. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, pp 355−393; (b) Hosomi, A.; Miura, K. Si(IV) Lewis acids. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008; Vol. 1, pp 469−516.

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(5) (a) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48–49. (b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762–2763.

(6) (a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668–3669. (b) Takasu, K.; Hosokawa, N.; Inanaga, K.; Ihara, M. *Tetrahedron Lett.* **2006**, *47*, 6053–6056. (c) Jung, M. E.; Ho, D. G. *Org. Lett.* **2007**, *9*, 375–378. (d) Cheon, C. H.; Yamamoto, H. *Tetrahedron Lett.* **2009**, *50*, 3555–3558.

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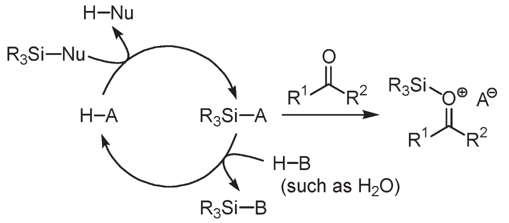
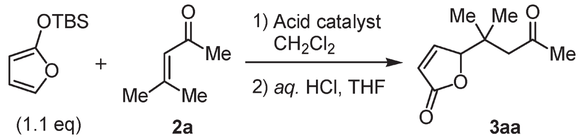
SCHEME 1. In Situ Generation of Silicon Lewis Acid "R_3Si-A" and Its Self Repairing



part "A" and I-strain between silyl part "R_3Si" and ligand part "A".[2b,7] Therefore, the design of Brønsted acid is a promising approach to develop catalytically active silicon species with high performance. Contrary to a design of Brønsted acid structure, Yamamoto and co-workers has already showed that the sterically bulky silyl part is an important factor for the catalytic activity of in situ generated silicon Lewis acid.[5] That is, $(Me_3Si)_3Si$-NTf_2 (Tf = CF_3SO_2) generated by the in situ reaction of nitrogen acid Tf_2NH with tris(trimethylsilyl)silyl (TTMS) enol ethers nicely catalyzes the Mukaiyama-aldol reaction of aldehydes with TTMS enol ethers, while the use of *t*-$BuMe_2Si$-NTf_2 generated from *tert*-butyldimethylsilyl (TBS) enol ethers instead of TTMS enol ethers resulted in a significant decrease in the yield of aldol products.

Recently, we reported aluminum methide complex Me_2Al-$CHTf_2$ prepared by the reaction of Me_3Al and bis(trifluoromethanesulfonyl)methane (Tf_2CH_2).[8] Since the Tf_2CH structure acts as a good proton donor due to *gem*-disubstitution by two triflyl groups, highly acidic $Tf_2CHC_6F_5$ was reported as a "super Brønsted acid" catalyst.[9,10] We have examined the synthetic applications of various carbon acids having the Tf_2CH group in the molecular structure. In this paper, we would like to report the vinylogous Mukaiyama−Michael (VMM) reaction[11] catalyzed by silyl methide species generated from 1,1,3,3-tetrakis(trifluoromethanesulfonyl)propane **1**[12,13] ($Tf_2CHCH_2CHTf_2$) having two acidic protons attached on the 1,3-carbons.[14] This is the first example of synthetic reactions catalyzed by carbon acid **1**.[15]

TABLE 1. Survey of Effective Acids for the Reaction of 2a with TBSO-Furan



entry	acid catalyst (mol %)	temp (°C)	time (h)	yield[a] (%)
1	$Tf_2CHCH_2CHTf_2$ **1** (0.25)	−78	2	88
2	$Tf_2CHCH_2CHTf_2$ **1** (0.05)	−78 to −24	3	87
3	Tf_2CH_2 (1.0)	−78	3	0
4	Tf_2CHMe (1.0)	−78	3	7
5	$Tf_2CHC_6F_5$ (0.05)	−78 to rt	5	36
6	TfOH (0.25)	−78	6	7
7	Tf_2NH (0.25)	−78	6	7
8	Me_3Al (40)	−78	3	64
9	none	rt	5	NR[b]

[a]Isolated yield. [b]No reaction.

Results and Discussion

1,1,3,3-Tetrakis(trifluoromethanesulfonyl)propane-Mediated VMM Reaction. At first, to survey the activity of the Tf group containing Brønsted acids, the reaction of 4-methyl-3-penten-2-one **2a** with TBSO-furan (1.1 mol equiv) as a model reaction was carried out (Table 1).[16] In the presence of 0.25 mol % of carbon acid **1**, the reaction at −78 °C for 2 h provided Michael adduct **3aa** in 88% yield after desilylation of silyl enol ether intermediate by aqueous HCl treatment (entry 1). The catalyst loading of **1** could be reduced to 0.05 mol % without significant decrease in the product yield (entry 2). Interestingly, Tf_2CH_2 did not catalyze this reaction (entry 3), while a weak catalyst activity was observed by replacing a hydrogen of Tf_2CH_2 with a methyl or C_6F_5 group. That is, the reactions in the presence of Tf_2CHMe (1.0 mol %) and $Tf_2CHC_6F_5$ (0.05 mol %) gave 1,4-adduct **3aa** in 7% and 36% yield, respectively (entries 4 and 5). Compared to the high activity of **1**, the efficiency of other Brønsted acids such as TfOH and Tf_2NH was remarkably lower. For instance, in the presence of 0.25 mol % of TfOH, Michael adduct **3aa** was obtained in only 7% yield (entry 6). The use of Tf_2NH also gave the essentially same result as in the case of TfOH (entry 7). Additionally, the use of Me_3Al instead of carbon acid **1** required a notable increase in catalyst loading, but resulted in a low yield of **3aa** (40 mol %, 64% yield) (entry 8). In the absence of acids, the reaction at room temperature also resulted in no change of **2a** and silyloxyfuran (entry 9). Despite a number of reports demonstrating that Lewis acid can promote 1,4-addition of silicon enolate to sterically crowded β,β-disubstituted enones via single-electron transfer mechanism,[17] the construction of quaternary carbon through Brønsted acid-mediated Michael-type addition to β,β-disubstituted enones has been limited.

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(7) (a) Mathieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219–8226. (b) Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561–9561.

(8) (a) Yanai, H.; Takahashi, A.; Taguchi, T. *Tetrahedron* **2007**, *63*, 12149–12159. (b) Yanai, H.; Takahashi, A.; Taguchi, T. *Tetrahedron Lett.* **2007**, *48*, 2993–2997.

(9) For examples of Brønsted acid catalysts equipped with an Tf_2CH group, see: (a) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4077–4079. (b) Ishihara, K.; Hasegawa, A.; Yamamoto, H. *Synlett* **2002**, 1299–1301. (c) Kokubo, Y.; Hasegawa, A.; Kuwata, S.; Ishihara, K.; Yamamoto, H.; Ikariya, T. *Adv. Synth. Catal.* **2005**, *347*, 220–224.

(10) For a chiral Brønsted acid catalyst equipped with an Tf_2CH group, see: Hasegawa, A.; Naganawa, Y.; Fushimi, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 3175–3178.

(11) Mukaiyama, T.; Matsuo, J. Boron and Silicon Enolates in Crossed Aldol Reaction. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 127−160.

(12) (a) Nozari, M. S. Ger. Patent 2609148, **1976**. (b) Siefken, M. W. Ger. Patent 2609150, **1976**. (c) Koshar, R. J.; Barber, L. L., Jr. U.S. Patent 4053519, **1977**.

(13) $Tf_2CHCH_2CHTf_2$ is a nonfuming and nonhydroscopic crystal. This compound can be stored at room temperature for several months without decomposition.

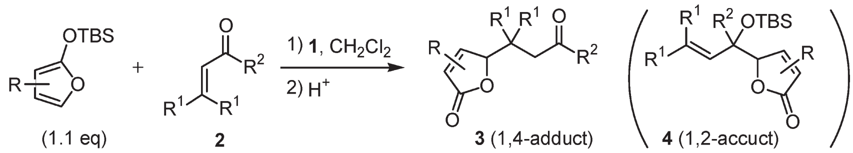
(14) Takahashi, A.; Yanai, H.; Taguchi, T. *Chem. Commun.* **2008**, 2385–2387.

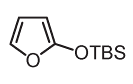
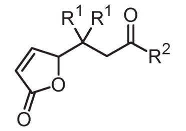
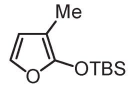
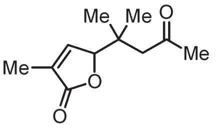
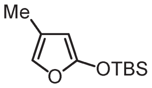
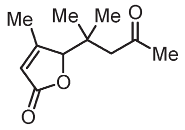
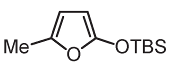
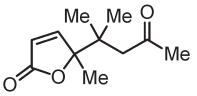
(15) Previously, in the field of polymer synthesis, carbon acid **1** had been used as a strong Brønsted acid catalyst, see: Robins, J.; Young, C. Ring-opening polymerization. In *ACS Symp. Ser.* **1985**, *286*, 263−274.

(16) For selected examples of the VMM reactions with heterocyclic dienoxysilane, see: (a) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525–1542. (b) Scettri, A.; De Sio, V.; Villano, R.; Acocella, M. R. *Synlett* **2009**, 2629–2632. (c) Barluenga, J.; de Prado, A.; Santamaría, J.; Tomás, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6583–6585. (d) Brimble, M. A.; Burgess, C.; Halim, R.; Petersson, M.; Ray, J. *Tetrahedron* **2004**, *60*, 5751–5758. (e) Arroyo, Y.; de Paz, M.; Rodríguez, J. F.; Sanz-Tejedor, M. A.; García Ruano, J. L. *J. Org. Chem.* **2002**, *67*, 5638–5643. (f) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223–1224.

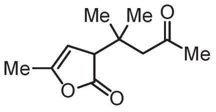
(17) Otera, J.; Fujita, Y.; Sakuta, N.; Fujita, M.; Fukuzumi, S. *J. Org. Chem.* **1996**, *61*, 2951–2962.

TABLE 2. Carbon Acid-Mediated VMM Reaction of α,β-Enone 2[a]



Entry	2-TBSO-furan	2	R^1	R^2	1 (mol%)	1,4-Adduct (3)		Yield^{b} (%)	Ratio^{c} (3/4)
1^{d}		2b	-(CH$_2$)$_5$-	Me	0.25		3ba	90	1,4-only
2^{d}		2c	H	Me	0.05		3ca	82	1,4-only
3^{e}		2d	H	Ph	0.10		3da	89	1,4-only
4^{e}		2e	H	4-BrC$_6$H$_4$	0.10		3ea	88	1,4-only
5^{d}		2a	Me	Me	0.25		3ab	86	42 : 1
6^{d}		2a	Me	Me	0.25		3ac	86	10 : 1
7^{d}		2a	Me	Me	1.00		3ad	72^{f}	1,4-only
8^{d}		2a	Me	Me	0.25		3ad	55^{g}	1,4-only

[a] Reaction temperature, −78 to −24 °C; reaction time 1−4 h. [b] Isolated yield. [c] Based on isolated yield. [d] Acidic workup by aq HCl in THF. [e] Acidic workup by TfOH in CH$_2$Cl$_2$. [f] 1,4-Adduct **5** was obtained in 25%. [g] 1,4-Adduct **5** was obtained in 29%.



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To see the scope of the present carbon acid-mediated VMM reaction, we examined the reaction of various α,β-enones with 2-TBSO-furans (Table 2). The reaction of cyclohexylideneacetone **2b** with 2-TBSO-furan was nicely promoted by 0.25 mol % of **1** to give 1,4-adduct **3ba** in 90% yield (entry 1). Methyl vinyl ketone **2c** and aryl vinyl ketone derivatives **2d**, **2e** were also found as good substrates for the present reaction (**3ca** 82% yield, **3da** 89% yield, and **3ea** 88% yield). Since catalyst loading was varied in a range from 0.05 to 0.25 mol % in these cases, excellent activity of propane diacid **1** was clearly demonstrated. In the presence of 0.25 mol % of **1**, the reaction of **2a** with 3-methyl-2-TBSO-furan smoothly proceeded at −78 °C to give 1,4-adduct **3ab** in 84% yield along with a small amount of 1,2-adduct **4ab** (2% yield) after acidic workup (entry 5). As shown in entry 6, in the case of 4-methyl-2-TBSO-furan, the 1,4-/1,2-selectivity was decreased to 10:1, although an excellent combined yield of **3ac** and **4ac** was observed (86% yield). Surprisingly, in the presence of 1.0 mol % of **1**, the reaction with 5-methyl-2-TBSO-furan gave 1,4-adduct **3ad**, which has consecutive quaternary carbons, in 72% yield without the formation of any 1,2-adducts. In this reaction, isomer **5** was also formed as a major byproduct (∼25% yield) (entry 7). Since, as shown in entry 8, lower catalyst loading of **1** (0.25 mol %) resulted in a significant decrease of the reaction rate and poor yield of **3ad**, more than 1 mol % of **1** was necessary to obtain a smooth reaction.

Carbon Acid-Mediated Diastereoselective VMM Reaction. Next, to realize an acyclic stereoselection in the carbon acid-catalyzed VMM reaction, we examined the reaction of benzalacetone **2f** with several 2-silyloxyfurans.[18,19] Selected results are summarized in Table 3. In the presence of 1.0 mol % of carbon acid **1**, the reaction of **2f** with 1.1 mol equiv of 2-TBSO-furan at −78 °C completed within 2 h to give 1,4-adduct **3fa** in 91% yield with poor *anti* selectivity (*anti*/*syn* = 1.8:1) (entry 1). Under the same conditions, 3-methyl-2-TBSO-furan and 3-bromo-2-TBSO-furan gave a better *anti* selectivity (entry 2, *anti*/*syn* = 4.9:1; entry 3, *anti*/*syn* = 16:1). Interestingly, the diastereoselectivity also

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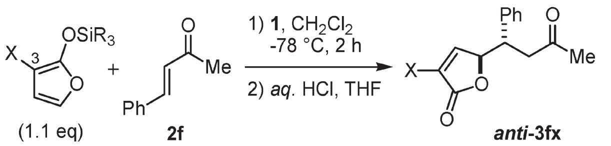
(18) For enantioselective and diastereoselective 1,4-addition of silyloxyfurans catalyzed by chiral Lewis acids, see: (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015–17028. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Synlett* **1997**, 568–570. (c) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203–10212. (d) Suga, H.; Kitamura, T.; Kekahi, A.; Baba, T. *Chem. Commun.* **2004**, 1414–1415. (e) Yang, H.; Kim, S. *Synlett* **2008**, 555–560.

(19) For enantioselective and diastereoselective 1,4-addition of silyloxyfurans catalyzed by chiral organocatalyst, see: Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194.

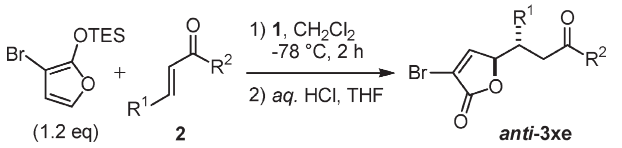
TABLE 3. Substituent Effects of Silyloxyfuran on Diastereoselectivity



entry	SiR$_3$	X	**1** (mol %)	**3fx**	yield[a] (%)	*anti*/*syn*[b]
1[c]	TBS	H	1.0	**3fa**	91	1.8:1
2[c,d]	TBS	Me	1.0	**3fb**	87	4.9:1
3[c]	TBS	Br	1.0	**3fe**	92	16:1
4[c]	SiEt$_2$*i*-Pr	H	1.0	**3fa**	91	3.6:1
5[c]	TES	H	1.0	**3fa**	93	5.0:1
6[c]	TES	Br	1.0	**3fe**	93	20:1
7[e]	TES	Br	0.5	**3fe**	95	> 30:1
8[e]	TES	Br	0.25	**3fe**	90	*anti* only
9[e]	TES	Br	0.25	**3fe**	89	> 30:1

[a] Isolated yield. [b] Based on ^{1}H NMR. [c] Concentration of **2f**: 0.25 M. [d] 1,2-Adduct was obtained in 6% yield. [e] Concentration of **2f**: 0.5 M.

TABLE 4. *Anti*-Selective VMM Reaction of 2 with 3-Bromo-2-TESO-Furan



entry	**2**	R^1	R^2	1 (mol %)	**3**	yield[a] (%)	*anti*/*syn*[b]
1	**2g**	Me	Me	0.5	**3ge**	76	12:1
2	**2h**	CH$_2$CH$_2$Ph	Me	0.25	**3he**	91	> 30:1
3	**2i**	*c*-Hex	Me	0.25	**3ie**	93	*anti* only
4[c]	**2i**	*c*-Hex	Me	0.25	**3ie**	0	
5[d]	**2j**	*c*-Hex	*t*-Bu	1.0	**3je**	66	8.5:1
6[e]	**2k**	Ph	Ph	1.0	**3ke**	95	> 30:1
7[f]	**2m**	CO$_2$Et	Me	0.5	**3me**	96	5.6:1
8[f]	**2n**	CO$_2$*i*-Pr	Me	0.5	**3ne**	80	6.5:1

[a] Isolated yield. [b] Based on ^{1}H NMR of crude mixture. [c] Tf$_2$NH was used instead of carbon acid **1**. [d] Reaction was carried out at −24 °C for 1 h. [e] Desilylation: TfOH, CH$_2$Cl$_2$, −78 °C, 0.5 h. [f] Stereochemistry is not determined

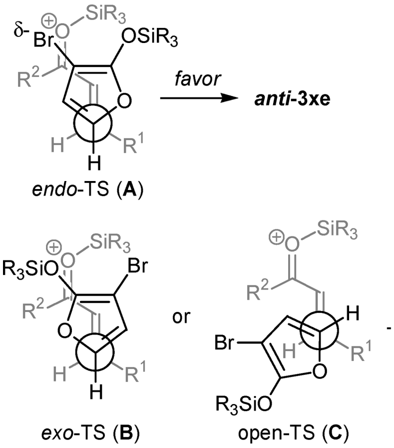


FIGURE 1. Possible transition state models of the VMM reaction.

depended on the steric bulkiness of the silyl group. Thus, 2-silyloxyfuran having a relatively less hindered silyl group such as 2-TESO-furan gave better diastereoselectivity (*anti*/*syn* = 3.6−5.0:1, entry 1 vs. entries 4 and 5). In the reaction with 3-bromo-2-silyloxyfurans, a similar tendency for the improvement of the diastereoselectivity by the relatively less hindered silyl group was also observed and 3-bromo-2-TESO-furan was found as a nice nucleophile for the *anti*-selective VMM reaction.[20] That is, in the presence of 1.0 mol % of carbon acid **1**, the reaction with 3-bromo-2-TESO-furan gave the 1,4-adduct **3fe** in 93% yield with excellent *anti*-selectivity (*anti*/*syn* = 20:1, entry 6). The relative configuration of the major diastereomer was determined as the *anti* relationship by an X-ray crystallographic analysis (see the Supporting Information). The loading of carbon acid catalyst also influenced the diastereoselectivity and, under higher substrate concentration conditions, a perfect *anti*-selectivity was realized by using 0.25 mol % of **1** without significant decreases in the product yield (entries 7 and 8). On the other hand, the use of 3-bromo-2-TBSO-furan instead of 3-bromo-2-TESO-furan resulted in a slight decrease in the *anti*-selectivity (entry 9).

To reveal the scope of the present *anti*-selective VMM reaction, we also conducted the reaction of various α,β-enones with 3-bromo-2-TESO-furan in the presence of 1.0 mol % or less than 1.0 mol % of carbon acid **1** (Table 4). In the reactions of methyl ketones (R^2 = Me) **2g**−**i**, less than 1.0 mol % of carbon acid **1** was effective enough to complete the reaction and 1,4-adducts **3ge**−**ie** were obtained in good yields with excellent *anti*-selectivities (entries 1−3). On the other hand, the reaction of enone **2i** with 3-bromo-2-TESO-furan did not proceed in the presence of Tf$_2$NH instead of **1** under the same conditions (entry 4). These results clearly showed the high activity of carbon acid **1**.[21] Since the silylation activity of "Et$_3$Si-A" is elevated by elongating the Si−A bond through steric repulsion between the relatively less hindered Et$_3$Si group and ligand part "A", highly hindered carbon acid **1** possibly performed as a better Brønsted acid precatalyst for this system.

While the reactivity of *tert*-butyl ketone **2j** was notably lower than that of methyl ketone **2i**, the desired 1,4-adduct **3je** was formed in 66% yield with reasonable diastereoselectivity by the reaction at −24 °C for 2 h in the presence of 1.0 mol % of 1,3-propane diacid **1** (entry 5). The use of at least 1.0 mol % of **1** was required for the reaction of phenyl ketone **2k** to give 1,4-adduct **3ke** in 95% yield with excellent *anti*-selectivity (*anti*/*syn* = >30:1, entry 6). Since Heathcock and co-workers reported that, in the TiCl$_4$-catalyzed Mukaiyama−Michael reaction of α,β-enone with simple ketene silyl acetals, good *syn*-selectivity was observed in the reaction of *tert*-butyl ketone,[22] the present *anti*-selectivity showed a sharp contrast in the substituent effect of the R^2 part. β-Alkoxycarbonylated α,β-enones **2m** and **2n**, which are susceptible to polymerization under acidic conditions, were also found to be nice substrates for this VMM reaction. By using 0.5 mol % of carbon acid **1**, 1,4-adducts **3me** and **3ne** were obtained in 96% and 80% yield,

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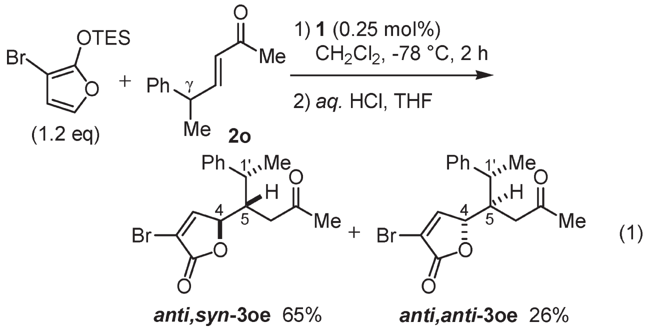
[20] For the Lewis acid-catalyzed vinylogous Mukaiyama-aldol reaction with 3-bromo-2-silyloxyfuran, see: López, C. S.; Álvarez, R.; Vaz, B.; Faza, O. N.; de Lera, Á. R. *J. Org. Chem.* **2005**, *70*, 3654–3659.

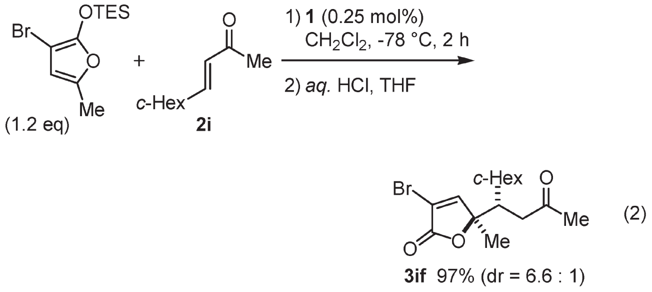
[21] In the presence of 1 mol % of 2,6-di-*tert*-butylpyridine, the VMM reaction of **2i** was catalyzed by 1.0 mol % of carbon acid **1**. This finding also supports that in situ generated silyl methide acts as a catalytically active species, see: Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581 and refs 4a and 6d.

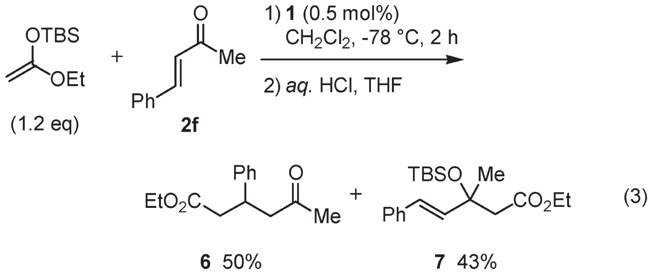
[22] (a) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797–2799. (b) Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1985**, *51*, 279–280.

respectively (entries 7 and 8). In each reaction, a high level of acyclic stereocontrol was observed.

As an extension using more complex substrates, we tried the reactions as shown in eqs 1 and 2. The reaction of **2o**, which has a stereogenic carbon center at the carbonyl γ-position, with 3-bromo-2-TESO-furan was nicely promoted by only 0.25 mol % of carbon acid **1** to give *anti,syn*-**3oe** and *anti,anti*-**3oe** in 65% and 26% yield, respectively, without the formation of the other diastereomers (eq 1). This result suggested that the VMM reaction of **2o** proceeds with perfect 4,5-*anti* selectivity and with moderate 5,1′-*syn* selectivity. Under the same conditions, the reaction of enone **2i** with 3-bromo-5-methyl-2-TESO-furan also gave the 1,4-adduct **3if** in 97% yield as a mixture of *anti*/*syn* isomers in a ratio of 6.6:1 (eq 2). In consequence, the present carbon acid-mediated VMM reaction is a highly effective methodology for the diastereoselective C−C bond formation between quaternary carbon and tertiary carbon.







Unfortunately, both theoretical and experimental studies on diastereoselectivity in the VMM reaction are limited.[23] However, since we found that, in the presence of carbon acid **1**, the reaction of benzalacetone **2f** with acyclic ketene silyl acetal proceeded in a nonregioselective manner to give a mixture of 1,4-adduct **6** and 1,2-adduct **7** (eq 3), we assume that the complete 1,4-selectivity observed in the reaction using 2-silyloxyfurans should be attributed to the secondary orbital interaction between silylated α,β-enone substrate and 2-silyloxyfuran in the transition state. That is, as shown in Figure 1, major *anti*-**3xe** was possibly formed via *endo* transition state **A**, similar to the Diels−Alder reaction under kinetic conditions. In addition, the electrostatic interaction between the electronically negative 3-bromo group on silyloxyfuran and the electronically positive oxocarbenium moiety of enone substrate should stabilize this *endo* transition state.

SCHEME 2. Synthetic Applications of α-Bromo-γ-butenolide 3if

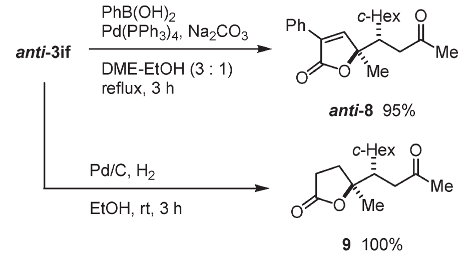
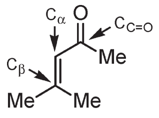


TABLE 5. Chemical Shifts of 2a in the Presence of Brønsted Acids in ^{13}C NMR[a]



2a

entry	Brønsted acid	chemical shifts[b] $C_{C=O}$	$\Delta C_{C=O}$	C_α	ΔC_α	C_β	ΔC_β
1	none	198.7		124.3		155.0	
2	TfOH	210.6	+11.9	122.8	−1.5	186.8	+31.8
3	$Tf_2CHCH_2CHTF_2$	199.3	+0.6	124.2	−0.1	155.5	+0.5
4	Tf_2CH_2	199.0	+0.3	124.2	−0.1	155.5	+0.5

[a] 0.5 M solution of **2a** and Brønsted acid in $CDCl_3$ at room temperature. [b] 100 MHz, ppm.

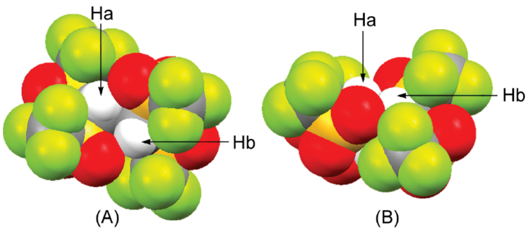


FIGURE 2. Space-filling projection of carbon acid **1** on the basis of X-ray crystallographic analysis: (A) top view and (B) side view.

To show the synthetic applications of α-bromo-γ-butenolide products, we carried out some transformations of *anti*-**3if** (Scheme 2).[24] For example, the Suzuki−Miyaura

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[23] (a) Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron* **2008**, *64*, 11697–11705. (b) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Reddy, N. S.; Reddy, P. J. *Tetrahedron Lett.* **2009**, *50*, 3760–3762.

[24] For synthetic applications of α-bromo-γ-butenolides, see: (a) Takei, H.; Fukuda, Y.; Sugaya, K.; Taguchi, T.; Kawahara, T. *Chem. Lett.* **1980**, 1307–1310. (b) Takei, H.; Fukuda, Y.; Taguchi, T.; Kawahara, T.; Mizutani, H.; Mukuta, T. *Chem. Lett.* **1980**, 1311–1314. (c) Olpp, T.; Brückner, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 1553–1557. (d) Vaz, B.; Domínguez, M.; Alvarez, R.; de Lera, A. R. *Chem.—Eur. J.* **2007**, *13*, 1273–1290.

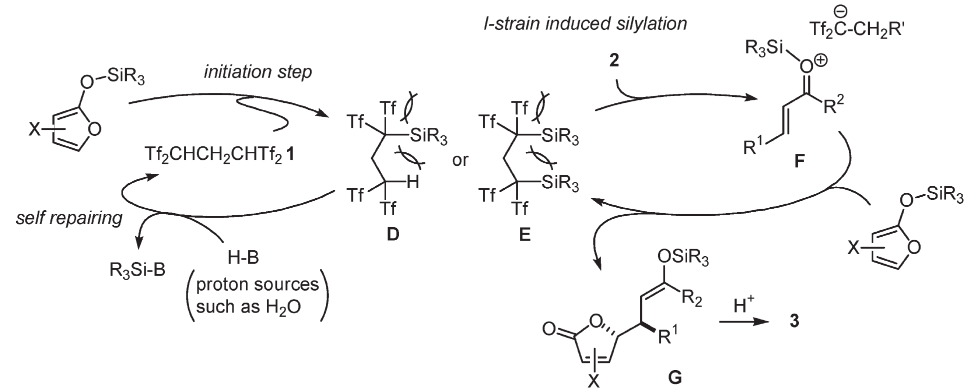

FIGURE 3. Proposed catalyst cycle of the carbon acid-mediated VMM reaction.

cross-coupling reaction of *anti*-**3if** with phenylboronic acid nicely proceeded under the standard conditions to give α-phenyl-γ-butenolide *anti*-**8** in 95% yield without epimerization.[25] Furthermore, the hydrogenation of *anti*-**3if** in the presence of palladium on carbon gave debrominated γ-butanolide **9** in quantitative yield.

The Origin of High Efficiency of Tetrakis(trifluoromethanesulfonyl)propane. Regarding excellent efficiency of 1,1,3,3-tetrakis(trifluoromethanesulfonyl)propane **1** for the VMM reaction of α,β-enones with 2-silyloxyfurans, we measured its acidity[26] to reveal the origin of the activity.

The gas-phase acidities established with use of the FT-ICR technique[27] were used as an extensive scale for strong Brønsted acids. In this scale, the acidities are expressed as ΔG_{acid} value of proton dissociation equilibrium and ΔG_{acid} values (kcal/mol) of some strong Brønsted acids are as follows: H_2SO_4 (302.2), TfOH (299.5), Tf_2NH (286.5), and Tf_2CH_2 (300.6).[27a,28] Since the experimental ΔG_{acid} value of carbon acid **1** was 295.7 kcal/mol, the acidity of **1** is stronger than those of H_2SO_4 and TfOH at the gas phase. However, a 1:1 mixture of carbon acid **1** and 4-methyl-3-penten-2-one **2a** in $CDCl_3$ did not show significant shifts of each signal in ^{13}C NMR compared to the case of TfOH (Table 5). For example, while the upfield shifts of $C_{C=O}$ and C_β were observed (entry 2: $\Delta C_{C=O} = +11.9$ ppm, $\Delta C_\beta = +31.8$ ppm) in the presence of a stoichiometric amount of TfOH, the upfield shifts of these signals in the cases of carbon acid **1** and Tf_2CH_2 were particularly small (entries 3 and 4). A similar tendency was also observed in ^1H NMR analysis (see the Supporting Information).

These results suggest that the electrophilic activation of α,β-enone substrates through hydrogen bonding or protonation by **1** is not a major factor to promote the present VMM reaction. In addition, since the stoichiometric reaction of carbon acid **1** with 2-silyloxyfuran in the absence of α,β-enone substrates resulted in a rapid polymerization of the temporarily formed γ-butenolides,[29] the catalytically active species in the VMM reaction system would be the silyl methide species generated by the reaction of **1** with 2-silyloxyfurans (external Brønsted acid *catalyzed* reaction).[30]

Next, we also conducted an X-ray crystallographic analysis of carbon acid **1**. As shown in Figure 2, the space-filling model of **1** demonstrated that, in the solid state, acidic protons H_a and H_b locate in the inside of the molecular structure, meanwhile, electronically negative atoms such as fluorines and oxygens occupy the outside. Carbon acid **1** totally formed the bowl-like structure equipped with two acidic protons in a cavity. Thus, the steric crowding around acidic protons in carbon acid **1** would be larger than those of commonly used Brønsted acids such as Tf_2NH and TfOH, and this would be similar even in the solution state.

On the basis of these facts, we propose a catalyst cycle of the present VMM reaction as shown in Figure 3. That is, in situ generated silyl methide species **D** or disilylated derivative **E** activates α,β-enone substrate **2** through carbonyl silylation to form oxocarbenium intermediate **F**.[30] The sequential C−C bond formation with 2-silyloxyfuran provides the Michael adduct **G** along with the regeneration of silyl methide **D** or **E**. Since catalytically active species **D** or **E** derived from sterically hindered carbon acid **1** should be highly destabilized by an appreciable I-strain between the R_3Si part and the methide ligand part, this carbonyl silylation step would proceed even under the significant low concentration of silyl methide species. In addition, a self-repairing pathway of catalytically active **D** or **E** would assist to realize the low loading of carbon acid **1**.

Conclusions

We found that 1,1,3,3-tetrakis(trifluoromethanesulfonyl)propane **1** is an excellent Brønsted acid precatalyst for the VMM reaction of α,β-unsaturated ketones with 2-silyloxyfurans. The present reaction would be an external Brønsted acid catalyzed C−C bond forming reaction and in situ generated silyl methide species "$R_3Si\text{-}CTf_2R$" probably performs as a catalytically active species for this reaction. Under the present conditions, significantly low loading of carbon

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[25] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

[26] Although it is possible that carbon acid **1** performs as a diprotic acid having two Tf_2CH groups, the first proton dissociation constant K_{a1} would play a central role in its acidity.

[27] (a) Koppel, I. A.; Taft, R. W.; Anvia, F.; Zhu, S.-Z.; Hu, L.-Q.; Sung, K.-S.; DesMarteau, D. D.; Yagupolskii, L. M.; Yagupolskii, Y. L.; Ignat'ev, N. V.; Kondratenko, N. V.; Volkonskii, A. Y.; Vlasov, V. M.; Notario, R.; Maria, P.-C. *J. Am. Chem. Soc.* **1994**, *116*, 3047–3057. (b) Koppel, I. A.; Burk, P.; Koppel, I.; Leito, I.; Sonoda, T.; Mishima, M. *J. Am. Chem. Soc.* **2000**, *122*, 5114–5124.

[28] The ΔG_{acid} values of Tf_2NH and Tf_2CH_2 were recently revised, see: Leito, I.; Raamat, E.; Kutt, A.; Saame, J.; Kipper, K.; Koppel, I. A.; Koppel, I.; Zhang, M.; Mishima, M.; Yagupolskii, L. M.; Garlyauskayte, R. Y.; Filatov, A. A. *J. Phys. Chem. A* **2009**, *113*, 8421–8424.

[29] For this reason, we could not observe silyl methide species by ^1H and ^{13}C NMR studies.

[30] For the generation of silyl methide "$Me_3Si\text{-}C(C_6F_5)Tf_2$" by the reaction of $C_6F_5CHTf_2$ with allyltrimethylsilane, see: Hasegawa, A.; Ishihara, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5731–5733.

acid **1** was realized in a range from 0.05 to 1.0 mol %. This result is one of the most important advantages compared to the other acid-catalyzed or -mediated C−C bond forming reactions with silicon enolates. In addition, the present carbon acid-mediated conditions can be applied to the C−C bond formation between sterically hindered substrates.

Experimental Section

Preparation of 1,1,3,3-Tetrakis(trifluoromethanesulfonyl)-propane (1). This compound was prepared by the reported procedure.[12b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (2H, t, J = 7.0 Hz), 5.83 (2H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 72.5, 119.3 (q, J_{C-F} = 329.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −9.5 (12F, s). The structure was confirmed by X-ray crystallographic analysis.

5-(1,1-Dimethyl-3-oxobutyl)furan-2(5*H*)-one (3aa). To a solution of carbon acid **1** in CH_2Cl_2 (0.25 mM solution, 1.0 mL, 0.25 μmol) was added a solution of **2a** (49 mg, 0.50 mmol) and *tert*-butyl(furan-2-yloxy)dimethylsilane (109 mg, 0.55 mmol) in CH_2Cl_2 (1 mL) at −78 °C over 10 min. After being stirred for 2 h at −24 °C, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$, then it was concentrated under reduced pressure. The resulting residue was treated by 1 M HCl aqueous solution (10 mL) in THF (10 mL) for 30 min at room temperature. The reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (3 × 20 mL), dried over anhydrous $MgSO_4$, and evaporated. Purification of the resulting residue by column chromatography on silica gel (hexane/EtOAc = 2:1) gave **3aa** (80.1 mg, 0.44 mmol, 88% yield). Colorless oil; IR (neat) ν 1754, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.17 (3H, s), 2.14 (3H, s), 2.40 (1H, d, J = 17.1 Hz), 2.69 (1H, d, J = 17.1 Hz), 5.26−5.28 (1H, m), 6.15 (1H, dd, J = 5.8, 2.1 Hz), 7.47 (1H, dd, J = 5.8, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 22.9, 31.7, 36.7, 50.2, 88.1, 122.3, 154.3, 172.8, 207.3; MS (ESI-TOF) *m*/*z* 183 $[M + H]^+$; HRMS calcd for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1021, found 183.1012. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.74; H, 7.70.

(*R)-3-Bromo-5-[(*S**)-3-oxo-1-phenylbutyl]furan-2(5*H*)-one (*anti*-3fe) and (*S**)-3-Bromo-5-[(*S**)-3-oxo-1-phenylbutyl]furan-2(5*H*)-one (*syn*-3fe).** According to the synthetic procedure for **3aa**, 1,4-adduct **3fe** was obtained in 93% yield (*anti*-**3fe**, 136 mg, 0.45 mmol; *syn*-**3fe**, 0.02 mmol, 7 mg) (Table 3, entry 6) by the reaction of **2f** (73 mg, 0.50 mmol) with (3-bromofuran-2-yloxy)-triethylsilane (166 mg, 0.60 mmol) in the presence of carbon acid **1** (2.8 mg, 5.2 μmol) in CH_2Cl_2 (1.0 mL) at −78 °C for 2 h. The stereochemistry of **3fe** was determined by an X-ray crystallographic analysis of *anti*-**3fe**. For *anti*-**3fe**: colorless crystals; mp 114.0−114.6 °C; IR (KBr) ν 3087, 3029, 1761, 1712, 1609, 1497, 1454, 984, 767, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s), 2.84 (1H, dd, J = 17.5, 8.0 Hz), 2.96 (1H, dd, J = 17.5, 5.4 Hz), 3.41 (1H, td, J = 7.7, 5.4 Hz), 5.03 (1H, dd, J = 7.7, 1.6 Hz), 7.07−7.16 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6, 44.3, 44.8, 85.0, 113.7, 128.0, 128.1, 129.1, 138.7, 151.8, 167.9, 205.5; MS (ESI-TOF) *m*/*z* 331 $[M + Na]^+$, 333 $[M + 2 + Na]^+$; HRMS calcd for $C_{14}H_{13}BrNaO_3$ $[M + Na]^+$ 330.9946, found 330.9953. Anal. Calcd for $C_{14}H_{13}BrO_3$: C, 54.39; H, 4.24. Found: C, 54.24; H, 4.35. For *syn*-**3fe**: colorless oil; IR (neat) ν 1771, 1714, 1606, 1454, 1153, 981, 765, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (3H, s), 2.92 (1H, dd, J = 18.2, 5.8 Hz), 3.20 (1H, dd, J = 18.2, 8.3 Hz), 3.74 (1H, ddd, J = 8.3, 5.8, 3.4 Hz), 5.28 (1H, dd, J = 3.4, 1.8 Hz), 7.08−7.13 (2H, m), 7.22−7.32 (3H, m), 7.34 (1H, d, J = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 42.7, 44.2, 83.6, 113.2, 128.0, 128.2, 128.9, 136.3, 151.5, 168.1, 206.2; MS (ESI-TOF) *m*/*z* 331 $[M + Na]^+$; HRMS calcd for $C_{14}H_{13}BrNaO_3$ $[M + Na]^+$ 330.9946, found 330.9956.

Acknowledgment. The authors thank Mr. Haruhiko Fukaya (Tokyo University of Pharmacy and Life Sciences) for X-ray crystallographic analysis of the VMM products.

Supporting Information Available: Detailed experimental procedure, compound characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.