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Switchable Reactions of Cyclopropanes with Enol Silyl Ethers. Controllable Synthesis of Cyclopentanes and 1,6-Dicarbonyl Compounds

Jian-Ping Qu, Chao Deng, Jian Zhou, Xiu-Li Sun, and Yong Tang*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032

tangy@mail.sioc.ac.cn

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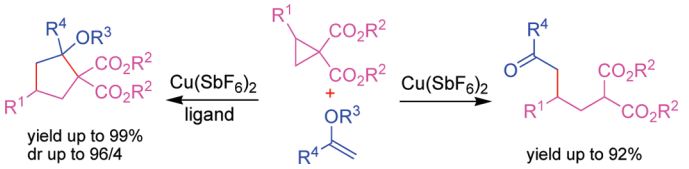

$Cu(SbF_6)_2$-catalyzed reaction of 2-substituted cyclopropane-1,1-dicarboxylates **1** with enol silyl ethers **2** can be readily controlled: the reaction undergoes a cycloaddition to provide substituted cyclopentane derivatives **3** in excellent yields with high diastereoselectivities in the presence of complex **8**/Cu(II); however, the same substrates afford acyclic 1,6-dicarbonyl products **4** via a cycloaddition−ring-opening reaction in up to 92% yield in the absence of ligand **8**. The mechanism for the ligand-switchable reactions was investigated by both control experiments and ^{1}H NMR studies. The substrate scope and limitation of the tunable transformation were also examined.

Introduction

The control of reaction pathways for selective synthesis of different products from the same starting materials[1−9] has attracted much attention since such research not only maximizes the diverse utility of reactants but also benefits the understanding of reaction mechanism. In our previous studies on this subject, we reported that HMPA could switch the stereochemistry of the cyclopropanation reaction of telluronium allylides with α,β-unsaturated esters and amides, providing a facile synthesis of two geometrical isomers of multifunctionalized 3-vinylcyclopropane derivatives.[2c]

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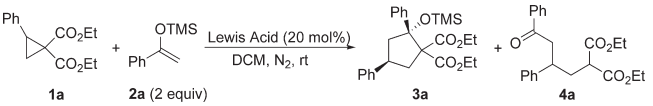
We also observed solvent-reversed enantioselectivity in the Friedel−Crafts reaction of indole with arylidene malonates catalyzed by trisoxazoline (TOX)-derived copper complex[5c] and temperature-controlled diastereoselectivity in the 1,3-dipolar cycloaddition of nitrones with arylidene malonates.[2k]

Donor−acceptor cyclopropanes have been frequently used in many synthetic transformations, owing to the unique reactivity of the cyclopropane moiety.[10−21] For example, these cyclopropanes can undergo various cycloadditions, such as the [3 + 2] cycloadditions with aldehydes,[11] aryl isocyanides,[12] cyanopyridine,[13] diazene derivatives,[14] imines[15] and indoles,[16] [3 + 3] cycloadditions with nitrones[17] and azomethine imines,[18] and [4 + 3] cycloadditions with isobenzofurans.[19] Among the cycloadditions developed, the reactions of cyclopropanes with enols are reported to afford cyclopentane derivatives and/or 1,6-dicarbonyl compounds, depending on substrates.[21,22] Very recently, we found that the product of cyclopropane-1,1-dicarboxylate with enol silyl ether can be tuned very well by ligand providing cyclopentanes[23] and 1,6-dicarbonyl compounds respectively with excellent selectivity. Herein, we wish to report the results in detail.

TABLE 1. Effects of Lewis Acids[a]



entry	Lewis acid	conv[b] (%)	**3a**/**4a**[b]	dr (**3a**)[b]
1	$Yb(OTf)_3 \cdot xH_2O$	53	99/1	82/18
2	$Sc(OTf)_3$	> 99	4/96	
3[21]	$In(OTf)_3$	> 99	11/89	
4	$Ga(OTf)_3$	> 99	8/92	
5	$Sn(OTf)_2$	> 99	4/96	
6	$Cu(OTf)_2$	91	1/99	
7	$Cu(SbF_6)_2$	> 99 (73[c])	1/99	
8	$FeCl_3$	27	67/33	87/13
9	$TiCl_4$[d]	36	1/99	

[a]Reaction conditions: **1a** (52.5 mg, 0.2 mmol), **2a** (76.9 mg, 0.4 mmol), Lewis acid (0.04 mmol), CH_2Cl_2 (1.0 mL), room temperature, 12 h. [b]Determined by ^1H NMR. [c]Isolated yield. [d]−78 °C, 24 h. When the reaction was performed at room temperature, the reaction was complicated.

Results and Discussion

Lewis Acid Effect. Using diethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** as a model substrate,[21] we first evaluated different Lewis acids as catalysts. The reaction of **1a** with enol silyl ether **2a** was performed in methylene chloride at room temperature under nitrogen atmosphere in the presence of 20 mol % of Lewis acid. For a clear comparison, reactions were all quenched after 12 h, followed by ^1H NMR analysis of the crude products. As shown in Table 1, Lewis acids influence strongly the reaction and the product distribution. For example, although metal perchlorate hydrates failed to promote the reaction,[24] metal triflates worked well in this reaction (entries 1−6). $Yb(OTf)_3 \cdot xH_2O$ afforded cycloaddition adduct **3a** as the sole product in moderate conversion with good diastereoselectivity (entry 1). The other triflates screened gave the ring-opening adduct **4a** as the main product in excellent conversion (entries 2−6). In particular, only product **4a** was obtained when $Cu(OTf)_2$ was used (entry 6). $Cu(SbF_6)_2$, prepared from $CuCl_2$ and

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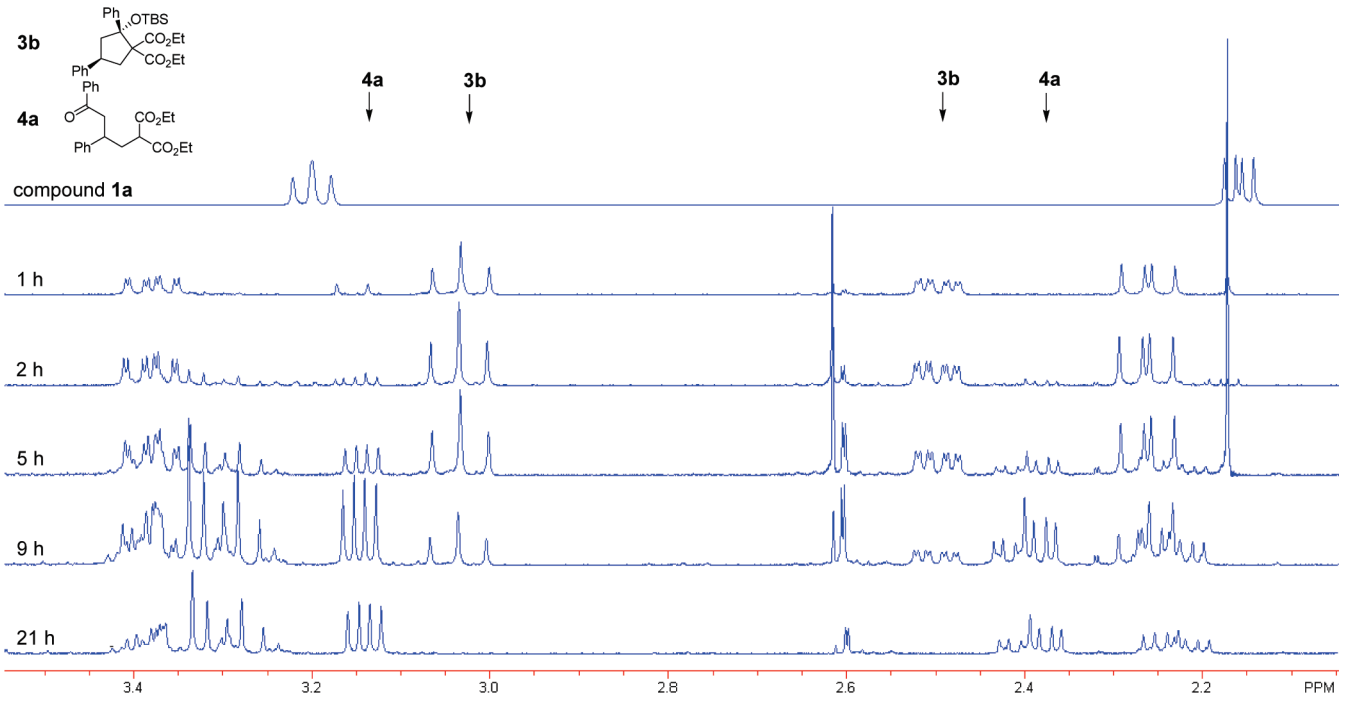
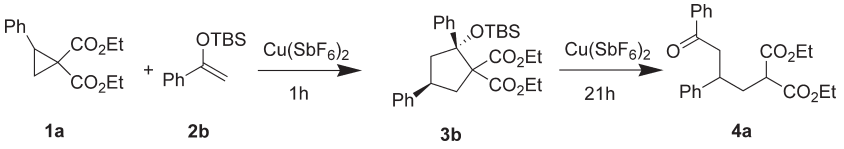


FIGURE 1. Monitoring the $Cu(SbF_6)_2$-catalyzed reaction between **1a** and **2b** in DCM by ^1H NMR.

SCHEME 1. Proposed Process of Cycloaddition−Ring-Opening Reaction

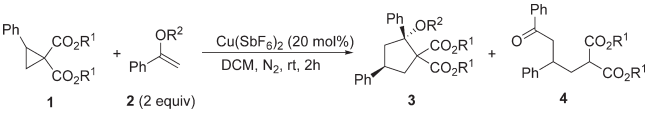


$AgSbF_6$ in situ,[25] could also promote the reaction to full conversion with a ratio of **4a**/**3a** up to 99/1 and product **4a** was isolated in 73% yield. Thus, the reaction product can be controlled by a simple choice of Lewis acid. To further improve the yield, we examined the effects of solvents, and methylene chloride (DCM) proved to be the optimal for the solvents screened.[24]

Since the product distribution is Lewis acid dependent, on the basis of the observation, we speculate that this reaction proceeds via a Lewis acid catalyzed [3 + 2] cycloaddition to afford product **3a**, which further gives product **4a** by a ring-opening reaction under the catalysis of the same Lewis acid, similar to the mechanism as Wang proposed.[21] To test this hypothesis, the effects of the ester group in cyclopropane **1** and the silyl group in enol silyl ether **2** on the reaction selectivity were examined by using $Cu(SbF_6)_2$ as a catalyst. As shown in Table 2, the bulky silyl group (TBS vs TMS) in compounds **2** slowed down the ring-opening reaction, affording cyclopentanes **3** as major products (entries 1−4, Table 2). The case of using ethyl ester **1a** and *tert*-butyl silyl ether **2b** as substrates gave product **3** with the satisfying selectivity (**3**/**4** up to 87/13 and dr up to 90/10) (entry 3).

To gain insight into the reaction pathway, ^1H NMR was used to monitor the reaction (Figure 1). As the ^1H NMR spectra demonstrated, cyclopropane (**1a**) disappeared in 1 h, and cycloaddition adduct **3b** (unique peaks at 3.03, 2.51 ppm) formed with a **3b**/**4a** ratio of >95/5. Two hours later, new signals appeared at 3.14 and 2.40 ppm, which correspond to the representative chemical shifts of acyclic compound **4a**. After 21 h, the product **3b** disappeared and was transformed into **4a** completely, suggesting that the reaction proceeded in a stepwise manner: the initial [3 + 2] cycloaddition afforded product **3b**, and then the following ring-opening reaction of **3b** gave product **4a** (Scheme 1).

TABLE 2. Effects of the Ester Groups in Cyclopropane 1 and the Silyl Groups in Enol Silyl Ether 2[a]



entry	R^1	R^2	conv[b] (%)	**3**/**4**[b]	dr (**3**)[b]
1	Et (**1a**)	TMS (**2a**)	>99	48/52	88/12
2	Me (**1b**)	TMS (**2a**)	>99	20/80	87/13
3	Et (**1a**)	TBS (**2b**)	>99	87/13	90/10
4	Me (**1b**)	TBS (**2b**)	>99	76/24	91/9

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $CuCl_2$ (5.4 mg, 0.04 mmol, 20%), $AgSbF_6$ (27.4 mg, 0.08 mmol), CH_2Cl_2 (1.0 mL), room temperature, 2 h. [b]Determined by ^1H NMR.

Effects of Ligand and Reaction Time. By ^1H NMR study and the experimental observation described above, there

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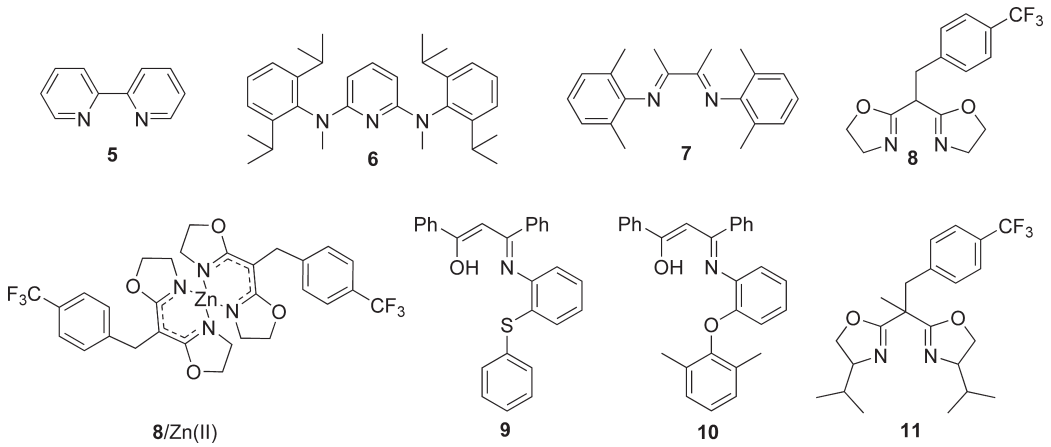
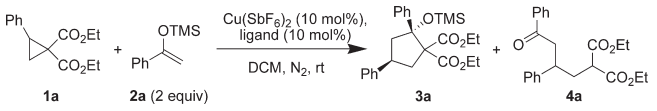


FIGURE 2. Ligands screened for the [3 + 2] cycloaddition.

TABLE 3. Effects of Ligand and Reaction Time on the Product Distribution of the Reaction of 1a with Enol Silyl Ether 2a[a]



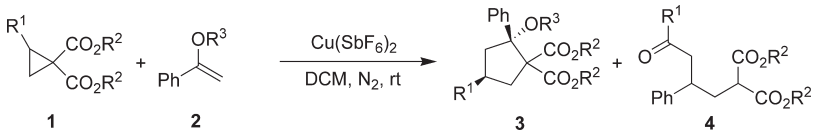
entry	Lewis acid	ligand	time (h)	conv[b] (%)	**3a**/**4a**[b]	dr (**3a**)[b]
1	$Cu(SbF_6)_2$	no	2	100	48/52	88/12
2	$Cu(SbF_6)_2$	no	12	100	< 1/99	
3	$Cu(SbF_6)_2$	Et_3N	24	0		
4	$Cu(SbF_6)_2$	pyridine	24	0		
5	$Cu(SbF_6)_2$	DBU	24	0		
6	$Cu(SbF_6)_2$	**5**	12	100	87/13	85/15
7	$Cu(SbF_6)_2$	**6**	24	< 1		
8	$Cu(SbF_6)_2$	**7**	24	54	96/4	92/8
9	no	**8**[c]	24	0		
10	$Cu(SbF_6)_2$	**8**[c]	24	85	> 99/1	94/6
11	$Cu(SbF_6)_2$	**8**[c]	48	100 (85[d])	> 99/1	94/6
12	$Cu(OTf)_2$	**8**	12	82	93/7	89/11
13	$Cu(SbF_6)_2$	**11**	24	100	> 99/1	92/8
14	$Cu(SbF_6)_2$	**9**	24	67	93/7	92/8
15	$Cu(SbF_6)_2$	**10**	24	19	> 99/1	86/14

[a]Reaction conditions: **1a** (52.5 mg, 0.2 mmol), **2a** (76.9 mg, 0.4 mmol), $CuCl_2$ (2.7 mg, 0.02 mmol, 10%), $AgSbF_6$ (13.7 mg, 0.04 mmol), ligand (0.02 mmol), CH_2Cl_2 (1.0 mL), room temperature, monitored by TLC for entries 1 and 2, $CuCl_2$ (5.4 mg, 0.04 mmol, 20 mol%), $AgSbF_6$ (27.4 mg, 0.08 mmol); [b]Determined by ^1H NMR; [c]Complex **8**/Zn(II) (6.2 mg, 0.009 mmol); [d]Isolated yield.

is possibility to tune the product by careful choice of the reaction time. As shown in Table 3, reaction time influences the product distribution strongly using $Cu(SbF_6)_2$ as a catalyst. For instance, a mixture of products **3a** and **4a** was obtained with a ratio of 48/52 when the reaction was quenched in 2 h, and only the ring-opening product **4a** was observed with a good stereoselectivity after 12 h of reaction (entry 1 vs 2). Since the Lewis acid catalysts proved to influence the reaction distribution (Table 1) and ligand can modulate the Lewis acidity of the catalyst, we envisioned that ligand might suppress the ring-opening reaction of product **3** in an easy way and also improve the diastereoselectivity of the cycloaddition reaction. Thus, we screened several nitrogen-containing ligands with different structures shown in Figure 2. As summarized in Table 3, monodentate ligands such as pyridine, Et_3N, and DBU failed to promote the reaction (entries 3−5). Pyridine derivative **6** is also inert (entry 7). Of the bidentate and tridentate ligands examined, ligands **7**, **9**, and **10** could promote the cycloaddition. Interestingly, when we tried to synthesize bisoxazoline **8** by a $Zn(OTf)_2$-mediated reaction between 2-aminoethanol and 2-(4-(trifluoromethyl)phenyl)malononitrile, only complex **8**/Zn(II) was obtained. Although the complex **8**/Zn(II) in the absence of $Cu(SbF_6)_2$ could not catalyze the cycloaddition (entry 9), the [3 + 2] cycloaddition reaction worked smoothly in the presence of catalytic **8**/Zn(II) and $Cu(SbF_6)_2$, and the ring-opening reaction was almost suppressed. In this case, the cycloaddition adduct **3a** was obtained in 85% yield with good diastereoselectivity (dr = 94/6) (entry 11). Both **8**/Zn(II) with $Cu(OTf)_2$ and **11**/ $Cu(SbF_6)_2$ could promote the reaction affording the desired product **3a** with good diastereoselectivity (entries 12 and 13).

Substrate Scope. Under the optimal conditions, we next evaluated the generality of this tunable reaction between enol silyl ethers with cyclopropanes. As shown in Table 4, the ester groups on cyclopropanes **1** slightly influenced the yields of the cycloaddition (entry 1 vs 3 and entry 2 vs 4, Table 4). Compared with TMS-protected enol, TBS-protected enol gave higher yield and better diastereoselectivity probably due to the steric hindrance. TIPS-protected enol silyl ethers diminished both the yield and diastereoselectivity. Thus, we chose the TBS-protected enol ethers for this study. All reactions of both electron-deficient and electron-rich 4-aryl cyclopropanes proceeded smoothly in excellent yields with good diastereoselectivities (entries 5−9). The cycloaddition reaction of styryl-substituted enol silyl ether gave the product **3j** in 78% yield with a diastereomeric ratio of 91/9 (entry 10). Diethyl 2-vinyl cyclopropane-1,1-dicarboxylates reacted smoothly, giving the desired product **3k** in moderate yield and diastereoselectivity (entry 11). 2-Furylcyclopropane gave complicated products at room temperature but underwent the reaction smoothly to afford the desired product **3l** in 65% yield at −45 °C. Raising the temperature to −25 °C improved the diastereoselectivity, but the yield decreased (entry 12). When the enol silyl ether was changed to (3,4-dihydronaphthalen-1-yloxy)trimethylsilane, two stereoisomers **3m** were isolated (entry 13). Silyl enol ether of phenyl ethyl ketone also worked very well, in which the two isomers could be separated in 55% and 24% yields. The structures of the products were determined by NMR. The

TABLE 4. Switchable Reactions of Cyclopropanes with Enol Silyl Ethers[a]



1 2 3 4

entry	R^1	R^2	R^3	with ligand		without ligand	
				product	yield (%)[b] (dr[c])	product	yield (%)[b]
1	Ph	Et	TMS	**3a**	85 (94/6)	**4a**	73
2	Ph	Et	TBS	**3b**	94 (96/4)	**4a**	80
3	Ph	Me	TMS	**3c**	73 (94/6)	**4b**	79[d]
4	Ph	Me	TBS	**3d**	99 (95/5)	**4b**	78
5	4-$CF_3C_6H_4$	Me	TBS	**3e**	94 (96/4)	**4c**	64
6	4-ClC_6H_4	Me	TBS	**3f**	98 (95/5)	**4d**	81
7	4-BrC_6H_4	Me	TBS	**3g**	99 (94/6)	**4e**	70
8	4-MeC_6H_4	Me	TBS	**3h**	99 (95/5)	**4f**	90
9	4-$MeOC_6H_4$	Me	TBS	**3i**	95 (95/5)	**4g**	92 (86[e])
10	Styryl	Me	TBS	**3j**	78 (91/9)	**4h**	49
11	Vinyl	Et	TBS	**3k**	85 (86/14)	**4i**	28 (51[f])
12	2-furyl	Me	TBS	**3l**	65[g] (80/20) 47[h] (90/10)	**4j**	15[i]
13	Ph	Et		**3m**	75 (46/54)	**4k**	47[j]
14	Ph	Et		**3n**	79[k]	**4l**	55[l]

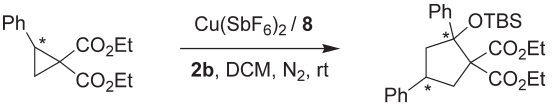
dr 15/1

[a]Method 1 (with **8**/Zn(II), for **3**): **1** (0.2 mmol), **2** (0.4 mmol), $CuCl_2$ (2.7 mg, 0.02 mmol, 10%), $AgSbF_6$ (13.7 mg, 0.04 mmol), complex **8**/Zn(II) (6.2 mg, 0.009 mmol), CH_2Cl_2 (1.0 mL), rt, monitored by TLC. Method 2 (without ligand, for **4**): **1** (0.2 mmol), **2** (0.4 mmol), $CuCl_2$ (5.4 mg, 0.04 mmol, 20%), $AgSbF_6$ (27.4 mg, 0.08 mmol), CH_2Cl_2 (1.0 mL), rt, monitored by TLC. [b]Isolated yield. [c]Determined by ^1H NMR using crude product before flash chromatography. [d]0.5 mmol scale. [e]1.0 mmol scale. [f]Trimethyl(1-phenylvinyloxy)silane was used instead of *tert*-butyldimethyl(1-phenylvinyloxy)silane. [g]$Cu(SbF_6)_2$/[**8**/Zn(II)] = 5 mol %/2.3 mol %, −45 °C. [h]$Cu(SbF_6)_2$/[**8**/Zn(II)] = 5 mol %/2.3 mol %, −25 °C. [i]−25 °C. [j]Two isomers obtained with a ratio of 70/30. [k]0.4 mmol scale. Isolated yields of two major isomers were 55% and 24%, respectively. [l]Two isomers obtained with a ratio of 75/25.

structure of **3d** was further confirmed by single-crystal X-ray diffraction analysis.[24] For the cycloaddition-ring-opening reaction of cyclopropanes **1** with enol silyl ethers **2**, the ester groups of cyclopropanes slightly influenced the yield of the reaction (entries 1−4, Table 4). The electronic character of the aryl group on the cyclopropanes had strong effects on the yields of the reaction (entries 5−9). Cyclopropanes with electron-withdrawing aryl groups gave the desired products in moderate yields (entries 5−7). Those with electron-donating groups underwent the ring-opening reactions smoothly in excellent yields (entries 8, 9). 2-Vinyl, 2-styryl, and 2-furylcyclopropane-1,1-dicarboxylates reacted with *tert*-butyldimethyl(1-phenylvinyloxy)silane affording the desired products in relatively low yields (entries 10−12). (3,4-Dihydronaphthalen-1-yloxy)trimethylsilane gave **4k** in 47% yield with poor diastereoselectivity (entry 13). Silyl enol ether of phenyl ethyl ketone also was a suitable substrate, and the reaction with cyclopropanes **1a** afforded cycloaddition-ring-opening diastereoisomers **4l** with a ratio of 75/25 (entry 14).

Noticeably, we used optically active **1a**[17e] with 77% ee instead of its racemic isomers to run the reaction with enol silyl ether **2b** in the presence of $Cu(SbF_6)_2$/**8**. It was found that the chirality was transferred to the product completely and cyclopentane derivative **3b** was obtained with 77% ee in 92% yield (Scheme 2).

SCHEME 2. [3 + 2] Reaction of Enol Silyl Ether 2b with Chiral Cyclopropane 1a



(-)-**1a,** 77% ee, (+)-**3b**, 92%, dr = 96/4, 77% ee

Conclusion

In summary, although the reaction of enol silyl ethers with 2-substituted cyclopropane-1,1-dicarboxylates has been reported to give 1,6-dicarbonyl compounds,[21] we have developed a strategy to control the products of this reaction by the choice of ligand/Lewis acid system. In the presence of ligand **8**/Zn(II), the cycloaddition between enol silyl ethers with

cyclopropanes catalyzed by $Cu(SbF_6)_2$ gave the pentasubstituted cyclopentane derivatives **3** with excellent diastereoselectivities in most cases. In the absence of the ligand, the same reaction afforded linear 1,6-dicarbonyl compounds. This method provides a good example for the reaction control. In addition, the mechanism for the current ligand-switchable reaction was investigated in detail by both control experiments and ^{1}H NMR studies. The mild reaction conditions, cheap and easily available catalyst, and the synthetically useful products make this method potentially useful in organic synthesis. Endeavors to develop the highly enantioselective version are now ongoing in our laboratory.

Experimental Section

Representative Procedure (with Ligand and 3a as an Example). To cyclopropane diester **1a** (52.5 mg, 0.20 mmol) was added a solution of $CuCl_2/AgSbF_6$ (2.7 mg, 0.02 mmol/13.7 mg, 0.04 mmol) and **8**/Zn(II) (6.2 mg, 0.009 mmol) in DCM (1.0 mL), followed by pumping of enol silyl ether **2a** (76.9 mg, 0.40 mmol), under nitrogen atmosphere. The resulting solution was stirred until the cyclopropane diester **1a** was completely consumed (48 h, monitoring by TLC, petroleum ether/ethyl acetate = 10/1, v/v). Then the mixture was passed through a short silica gel column and eluted with CH_2Cl_2 (50 mL). The combined elution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, v/v, 50/1) to give the pure **3a** as colorless oil: yield 65.9 mg (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 6.9 Hz, 2H), 7.43−7.23 (m, 8H), 4.38−4.21 (m, 2H), 3.85−3.66 (m, 3H), 3.35 (dd, J = 8.4, 13.5 Hz, 1H), 3.07 (t, J = 12.6 Hz, 1H), 2.42 (dd, J = 5.1, 12.6 Hz, 1H), 2.27 (dd, J = 10.8, 13.5 Hz, 1H), 1.37 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H), −0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 169.1, 143.5, 142.1, 128.5, 128.2, 127.5, 127.4, 127.1, 126.5, 88.9, 71.3, 61.1, 60.9, 47.6, 42.8, 41.5, 14.1, 13.5, 1.7; LRMS-ESI (m/z) $[M + Na]^+$ 477.1; HRMS-ESI $[M + Na]^+$ calcd for $C_{26}H_{34}O_5SiNa$ 477.2068, found 477.2075; IR (KBr, cm^{-1}) 3062, 3029, 2981, 2958, 2903, 1732, 1604, 1497, 1448, 1367, 1252, 1100, 1072, 987, 844, 755, 699.

Representative Procedure (without Ligand and 4a as an Example). To an oven-dried Schlenk reaction tube were added cyclopropane diester **1a** (52.5 mg, 0.20 mmol), $CuCl_2$ (5.4 mg, 0.04 mmol), $AgSbF_6$ (27.4 mg, 0.08 mmol), and CH_2Cl_2 (1.0 mL), followed by enol silyl ethers **2b** (93.7 mg, 0.40 mmol) under nitrogen atmosphere. The resulting mixture was stirred at room temperature for 23 h. After the reaction was complete (monitoring by TLC), the solution was passed through a short silica gel column, which was further eluted with CH_2Cl_2 (50 mL). The combined elution was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, v/v, 10/1) to give the pure **4a** as colorless oil: yield 76.5 mg (80%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.32−7.18 (m, 5H), 4.22 (q, J = 7.2 Hz, 2H), 4.12−3.96 (m, 2H), 3.44−3.23 (m, 3H), 3.14 (dd, J = 5.1, 9.9 Hz, 1H), 2.44−2.35 (m, 1H), 2.28−2.18 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 169.3, 169.2, 142.6, 136.9, 133.0, 128.6, 128.5, 128.0, 127.8, 126.9, 61.4, 61.3(7), 50.1, 45.7, 38.9, 35.0, 14.1, 13.9; LRMS-ESI (m/z) $[M + Na]^+$ 405.0; HRMS-ESI $[M + Na]^+$ calcd for $C_{23}H_{26}O_5Na$ 405.1672, found 405.1679; IR (KBr, cm^{-1}) 2957, 2924, 2851, 1731, 1688, 1449, 1371, 1268.

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Supporting Information Available: CIF files and crystallographic data, general synthetic procedures and characterization, and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.