JOC*Note*

Lewis Acid Catalyzed Reaction of Methylenecyclopropanes with 1,2-Diphenyldiselane or 1,2-Di-*p*-tolyldisulfane

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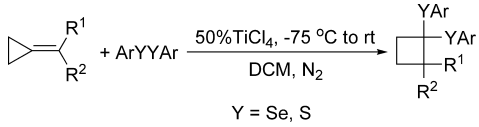
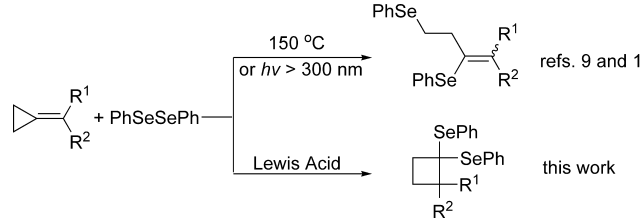


Catalyzed by Lewis acid, 1,2-diphenyldiselane or 1,2-di-*p*-tolyldisulfane could add to methylenecyclopropanes smoothly. Compared with the reported free radical additions, the results were quite different. A four-membered carbon ring was constructed to give cyclobutane-1,1-diylbis(phenylselane) derivatives or cyclobutane-1,1-diylbis(*p*-tolylsulfane) derivatives as products, which are useful intermediates in organic synthesis.

Methylenecyclopropanes (MCPs), which are highly strained but readily accessible molecules,[1] are useful building blocks in organic synthesis.[2] Because of the intramolecular ring strain, MCPs are highly activated and can undergo a series of particular and interesting reactions under mild conditions, providing novel methods for the construction of important organic skeletons. During the past decade, much attention has been paid to reactions involving MCPs. These include electrophilic additions,[3] free radical additions,[4] and transition metal catalyzed reactions.[5] Lewis acid catalyzed reactions of MCPs have also been widely investigated, involving the addition of alcoholic or acidic nucleophiles,[6a] aromatic amides,[6b] imines,[6c] activated aldehydes or ketones,[6d] arenes,[6e,f] acyl chlorides,[6g] and so on.[6h−k]

SCHEME 1. Addition of PhSeSePh to MCPs



Because of their wide applications in drug chemistry and organic synthesis, selenium-containing organic compounds are important and have attracted chemists for a long period.[7] Ordinarily, the addition of 1,2-diphenyldiselane to an unsaturated carbon carbon bond is a convenient way of introducing selenium.[8] In the investigation field of MCPs, the reactions with 1,2-diphenyldiselane have already been reported in the literatures, via heat-promoted[9] or visible-light-irradiated[10] free radical additions, affording a facile path for the synthesis of but-3-ene-1,3-diylbis(phenylselane) derivatives (Scheme 1). Herein, we wish to report the Lewis acid catalyzed additions of 1,2-diphenyldiselane to MCPs. Compared with the reported investigations, the reaction products were quite different (Scheme 1).

Initially, we examined the addition of 1,2-diphenyldiselane to MCP **1a** catalyzed by $AlCl_3$. When **1a**, 1,2-diphenyldiselane. and $AlCl_3$ were stirred in cyclohexane under nitrogen atmosphere protection, a novel cyclobutane structure unit containing

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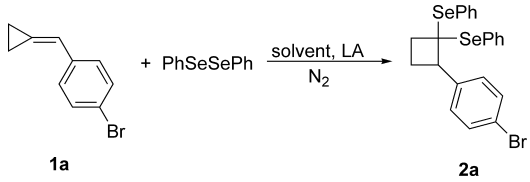
TABLE 1. Lewis Acid Catalyzed Addition of PhSeSePh to 1a under Different Conditions[a]



1a 2a

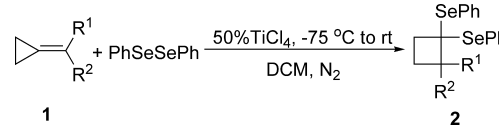
entry	LA[b] (equiv)	temp; time[c]	solvent	yield of **2a** (%)[d]
1	$AlCl_3$ (1)	rt; 24 h	cyclohexane	24
2	$AlCl_3$ (1.5)	rt; 20 h	cyclohexane	31
3	$AlCl_3$ (2)	rt; 18 h	cyclohexane	46
4	$AlCl_3$ (2)	50 °C; 4 h	cyclohexane	17
5	$TiCl_4$ (0.5)	rt; 1 h	DCM	15
6	$TiCl_4$ (0.5)	−25 °C to rt; overnight	DCM	38
7	$TiCl_4$ (0.5)	−75 °C to rt; overnight	DCM	62
8	$TiCl_4$ (1)	−75 °C to rt; overnight	DCM	35
9	$TiCl_4$ (10)	−75 °C to rt; overnight	DCM	traces
10	$FeCl_3$ (1)	rt; 24 h	cyclohexane	traces
11	BF_3OEt_2 (0.5)	−75 °C to rt; overnight	ether	traces

[a] 0.22 mmol of **1a** (10% excess), 0.2 mmol of 1,2-diphenyldiselane, and 1 mL of solvent were employed. [b] LA = Lewis acid. Purity of $AlCl_3$ was 99%. [c] The reaction was monitored by TLC (eluent, petroleum ether). [d] Isolated yields based on $(PhSe)_2$.

compound **2a** could be separated in 17−46% yield depending on the reaction conditions (entries 1−4, Table 1). Further screening demonstrated that $TiCl_4$ should be a better catalyst (entries 5−9, Table 1), and the yield of **2a** was enhanced to 62% yield by stirring the substrates with 50% $TiCl_4$ in dichloromethane (DCM) from −75 °C to rt (entry 7, Table 1).

Four-membered carbon ring structures are widely present in natural products.[11] They are of important value[12] but not easy to build due to the high ring strain. Containing a four-membered carbon ring and selenium element, cyclobutane-1,1-diylbis(phenylselane) derivatives are useful intermediates that serve important roles in organic synthesis and drug chemistry.[13] Hence, we tried to examine the application scope of this reaction under the optimized conditions outlined above, and the results are listed in Table 2. It is obvious that the corresponding product **2** could be synthesized smoothly when R^1 and R^2 are alkyl, aryl, or H (entries 1−9, Table 2). When R^1 and R^2 were both aryl, the yield decreased and the HCl adduct 1,1-diphenyl-4-chrolo-1-butene **3** (Figure 1) could be obtained in 38% yield as a result of the reaction of $TiCl_4$ with MCPs (entry 10, Table 2).[14] The structures of **2** were confirmed by single-crystal X-ray diffraction determination of **2i**, and the molecular structure of **2i** in crystal is shown in Supporting Information. For comparison to MCPs, methylenecyclobutanes (MCBs) are also highly strained molecules. However, when (4-bromophenyl) methelyenecyclobutane was employed, only a series of unidentified mixtures were observed instead of the desired ring enlargement product.

TABLE 2. Synthesis of Cyclobutane-1,1-diylbis(phenylselane) Derivatives (2)



1 2

entry	R^1, R^2	yield of **2** (%)[a]
1	*p*-BrC_6H_4, H (**1a**)	62 (**2a**)
2	C_6H_5, H (**1b**)	57 (**2b**)
3	*p*-ClC_6H_4, H (**1c**)	50 (**2c**)
4	C_7H_{15}, H (**1d**)	73 (**2d**)
5	C_9H_{19}, H (**1e**)	68 (**2e**)
6	-$CH_2CH_2CH(Ph)CH_2CH_2$- (**1f**)	71 (**2f**)
7	-$(CH_2)_5$- (**1g**)	47 (**2g**)
8	-$(CH_2)_6$- (**1h**)	40 (**2h**)
9	C_6H_5, C_5H_{11} (**1i**)	53 (**2i**)
10	C_6H_5, C_6H_5 (**1j**)	<10 (**2j**)

[a] Isolated yields.

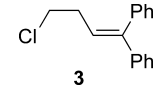


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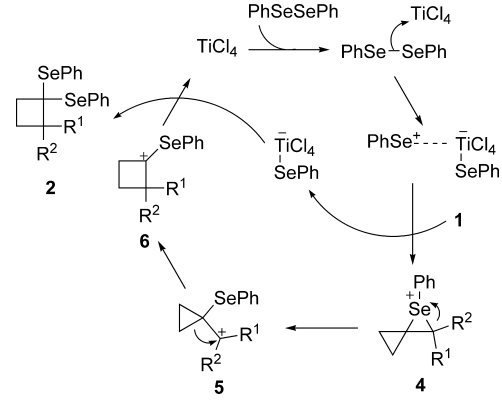
FIGURE 1. Structure of 1,1-diphenyl-4-chrolo-1-butene (**3**).

SCHEME 2. Possible Mechanism for the Lewis Catalyzed Addition of PhSeSePh to MCPs



On the basis of the above experimental results, a possible mechanism of this reaction is outlined in Scheme 2. The reaction of 1,2-diphenyldiselane with $TiCl_4$ affords the phenylselenyl cation, which adds to MCPs **1** and gives the intermediate **4** as the episelenium ion.[3c] The latter could be transformed to the intermediate carbon cation **5**, which rearranges to give the stable cyclobutyl cation **6**.[15] Further nucleophilic attack of $PhSe^-$ to **6** provides the final product **2**. The relief of the ring strain of MCPs should be the necessary thermodynamic driving force of this reaction. When simple olefins (e.g., cyclohexene) were employed, no reaction was observed.

1,2-Di-*p*-tolyldisulfane has reaction properties similar to those of 1,2-diphenyldiselane, and the addition of 1,2-di-*p*-tolyldisulfane to carbon−carbon unsaturated bonds is a facile method for the synthesis of sulfur-containing organic compounds, which are useful intermediates in organic synthesis and drug design.[16] Therefore, we next examined the addition of 1,2-di-*p*-tolyldisulfane to MCPs catalyzed by Lewis acid. Under similar

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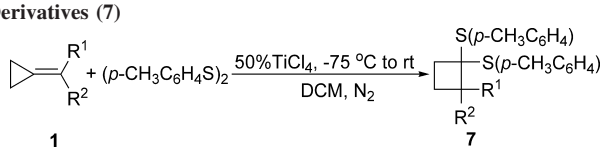
TABLE 3. Synthesis of Cyclobutane-1,1-diylbis(*p*-tolylsulfane) Derivatives (7)

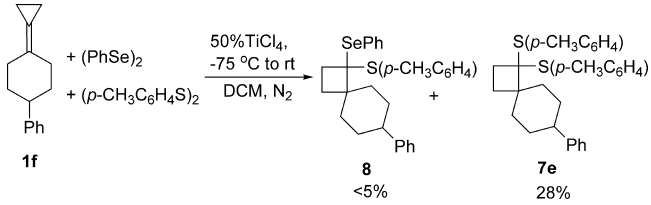


1 7

entry	R^1, R^2	yield of **7** (%)[a]
1	*p*-BrC_6H_4, H (**1a**)	75 (**7a**)
2	C_6H_5, H (**1b**)	68 (**7b**)
3	C_7H_{15}, H (**1d**)	72 (**7c**)
4	C_9H_{19}, H (**1e**)	88 (**7d**)
5	-CH_2CH_2CH(Ph)CH_2CH_2- (**1f**)	70 (**7e**)
6	-$(CH_2)_5$- (**1g**)	54 (**7f**)

[a] Isolated yields.

SCHEME 3. Difunctional Reaction of MCP 1g with (ArS)-(ArSe) Binary System Catalyzed by Lewis Acid



conditions as above, the desired products cyclobutane-1,1-diylbis(*p*-tolylsulfane) derivatives **7** could be synthesized conveniently from the corresponding MCPs in acceptable to good yields (Table 3).

Allowing the introduction of two different functional groups at the same time, difunctional reactions are important in organic synthesis.[17] Previously, Ogawa and co-workers developed a series of free radical mediated difunctional reactions employing a $(ArS)_2$-$(ArSe)_2$ binary system, which could introduce ArS and ArSe groups simultaneously.[8b−d,g] Encouraged by these works, we tried to examine our reaction of MCP **1f** with $(ArS)_2$ and $(ArSe)_2$. However, when the corresponding substrates were stirred together in the presence of $TiCl_4$, only traces of the difunctional product **8** were observed (Scheme 3).

In conclusion, we have developed a convenient method for the synthesis of substituted cyclobutane-1,1-diylbis (phenylselane) derivatives or cyclobutane-1,1-diylbis(*p*-tolylsulfane) derivatives via the addition of 1,2-diphenyldiselane or 1,2-di-*p*-tolyldisulfane to MCPs catalyzed by Lewis acid. A plausible mechanism has been proposed based on the above experimental results and previous reports. The novelty in this paper is the formation of the four-membered carbon ring, which is of synthetic value but not easy to obtain due to its high ring strain. Further investigations on the applications of these derivatives are being undertaken in our laboratory.

Experimental Section

General Procedure for the Lewis Acid Catalyzed Additions of 1,2-Diphenyldiselane or 1,2-Di-*p*-tolyldisulfane to MCPs. In a Schlenk tube, 0.22 mmol of **1** and 0.2 mmol of 1,2-diphenyldiselane (or 1,2-di-*p*-tolyldisulfane) were dissolved in 0.5 mL of DCM under nitrogen atmosphere. The mixture was kept at −75 °C, and 0.5 mL of $TiCl_4$ solution (0.2 mol/L) was added dropwise at this temperature. The reaction liquid turned red immediately and was stirred overnight. The temperature rose gently to room temperature. Water (5 mL) was then added, and the mixture was extracted with DCM (3 × 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was isolated by preparative TLC (eluent, petroleum ether/EtOAc 10:1) to give the corresponding product **2** or **7**.

Compound 2a. Oil. IR (film): 2950, 1435, 1232, 1071, 1009, 911, 822, 741, 692 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ 7.23−7.71 (m, 14H), 3.76−3.78 (m, 1H), 2.57−2.62 (m, 1H), 2.22−2.25 (m, 1H), 2.06−2.09 (m, 1H), 1.93−1.96 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.2, 31.7, 49.0, 55.6, 121.0, 128.0, 128.5, 128.7, 128.8, 129.2, 129.3, 130.2, 131.1, 136.7, 137.9, 138.6. MS (EI, 70 eV): *m*/*z* (%) 522 (1) [M^+], 365 (14) [M^+ − PhSe], 340 (76) [M^+-*p*-$BrC_6H_4CHCH_2$], 183 (88), 128 (100). HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}BrNaSe_2$ $(M + Na)^+$ 544.8898, found 544.8889.

Compound 7a. Oil. IR (film): 2960, 1628, 1483, 1394, 1241, 915, 811, 738 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, TMS): δ 7.10−7.47 (m, 12H), 3.74−3.77 (m, 1H), 2.48−2.51 (m, 1H), 2.37 (s, 3H), 2.34 (s, 3H), 1.97−2.08 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.7, 21.2, 21.3, 30.1, 48.4, 66.9, 120.8, 128.3, 129.3 (d), 129.6, 129.9, 131.0, 135.6, 137.1, 137.8, 138.5, 139.5. MS (EI, 70 eV): *m*/*z* (%) 454 (2) [M^+], 333 (9) [M^+ − $CH_3C_6H_4S$], 272 (100) [M^+ − *p*-$BrC_6H_4CHCH_2$]. HRMS (EI): *m*/*z* calcd for $C_{24}H_{23}BrS_2$ 454.0425, found 454.0421.

Acknowledgment. This work was supported by the National Natural Scientific Foundation of China (No. 20633010 and 20773106). We thank Prof. C. G. Yan and Miss L. T. Du for X-ray diffraction analysis.

Supporting Information Available: Single-crystal X-ray diffraction data of **2i** have been deposited with the CCDC (deposition no. CCDC 729806). General experimental procedures and spectroscopic data for all compounds, including crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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