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Convenient method for the addition of disulfides to alkenes

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Abstract—Catalytic disulfenylation reaction of alkenes by common Lewis acids has been investigated in detail. While reactions by $FeCl_3$ were feasible with cycloalkenes and other simple alkenes, much faster and excellent conversions were possible by $AlCl_3$ even with the substrates less reactive towards $FeCl_3$.

Introduction of sulfur functionality into unsaturated organic molecule is an important process for the drug development and other purpose of fine chemical synthesis.[1] We report herein a convenient method for the addition of disulfide to alkene, in the presence of a catalytic amount of common Lewis acids without using large excess amount of alkenes. The addition of disulfides to alkenes is a simple and reliable way for the synthesis of various sulfur-containing compounds. Recent reports on this type of reaction have revealed the utility of mild acid catalysts, either in a stoichiometric or a catalytic amount, which includes $BF_3{\cdot}OMe_2$,[2] PhIO-TfOH,[3] and $GaCl_3$[4] or a catalytic amount of a transition metal complex such as [CpRuCl(cod)].[5] Another report also emphasized the utility of metal cation-exchanged montmorillonites (M^+-monts).[6] These results prompted us to describe our own results for the comparison of the reagent ratio (alkene/disulfide) and effectiveness of the common catalysts such as aluminum chloride ($AlCl_3$) and ferric trichloride ($FeCl_3$).

According to the reaction mechanism discussed previously,[2] desired alkene disulfenylation should proceed via S-substituted disulfanium ion **3** or advanced S-substituted trisulfanium ion **4**, both of which are generated from Lewis acid (LA) and disulfide **2**, as shown in Figure 1. On the other hand, free-Lewis acid (LA) catalyzed *undesired alkene self-polymerization* as a competitive pathway. Due to the consumption of alkene **1** by this self-polymerization, a large excess amount of alkene was employed generally to attain the high conversion of

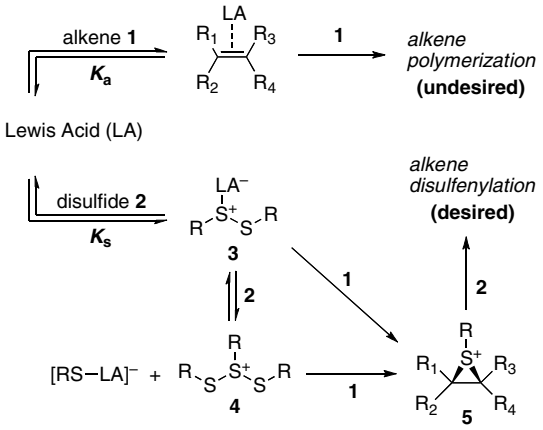

Figure 1. General reaction mechanism of Lewis acid catalyzed alkene disulfenylation.

disulfide **2**. For example, two equivalents of alkene were employed in the reaction of $BF_3{\cdot}OR_2$[2] and $GaCl_3$,[4] while in the reaction with M^+-monts, 6-fold excess of alkene was employed.[5] Because the selectivity between desired disulfenylation and undesired alkene self-polymerization would depend on the equilibrium constants (K_s and K_a), a *sulfur-favored* Lewis acids ($K_s \gg K_a$) would effectively promote the desired disulfenylation and accordingly prevent undesired alkene self-polymerization. On the other hand, the co-operative catalyst (PhIO-TfOH)[3] effectively catalyzed alkene disulfenylation with just one equivalent of alkene, while the catalyst was not enough inexpensive and stable.

We thus examined the activity of common Lewis acid catalysts for the alkene disulfenylation with least amount of alkenes **1** (1.2 equiv) and initial results are

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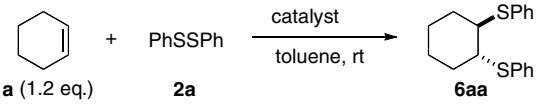
summarized in Table 1. With 10 mol% of trifric acid the alkene self-polymerization proceeded quite immediately, resulting in the low yield of desired product **6aa** (entry 1). Although $BF_3{\cdot}OEt_2$ effectively catalyzed the alkene disulfenylation as reported previously[2] (entry 2), the aluminum chloride showed the higher reactivity (5 mol% in entry 3, 3 mol% in entry 4). Ferric chloride was similarly effective to attain the highest conversion, while somewhat longer reaction time was required (entry 5). Other metals such as $FeCl_3{\cdot}6(H_2O)$, $CoCl_2$, $CuCl_2$, $Bi(NO_3)_3$ and $Yb(OTf)_3$ were all ineffective (entry 6–10). Toluene was most convenient for the reaction solvent, while other halogenated solvents such as CH_2Cl_2 and $ClCH_2CH_2Cl$ showed similar tendency. However, in coordinating solvents, reactions resulted in complete recovery of the starting disulfides, such as tetrahydrofuran (THF), diethyl ether, and cyclopentyl methyl ether (CPME).

Table 1. Acid catalyzed alkene disulfenylation



1a (1.2 eq.) **2a** **6aa**

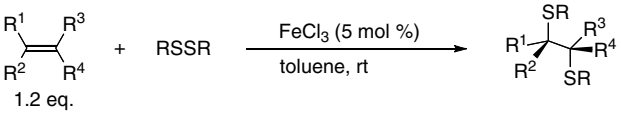
Entry	Catalyst	Loading (mol%)	Time (h)	% Yield
1	HOTf	10	0.5	35
2	$BF_3{\cdot}OEt_2$	5	4	72
3	$AlCl_3$	5	3	90
4	$AlCl_3$	3	6	95
5	$FeCl_3$	5	20	98
6	$FeCl_3{\cdot}6(H_2O)$	10	24	0
7	$CoCl_2$	10	24	0
8	$CuCl_2$	10	24	0
9	$Bi(NO_3)_3$	10	24	0
10	$Yb(OTf)_3$	10	24	3

From the initial screening, we were particularly interested in the behavior of $AlCl_3$ and $FeCl_3$. Both catalysts were most effective and notably, complete conversions have been attained with $FeCl_3$ under mild conditions. While these catalysts are very common in classical Lewis-acid catalyzed reactions, they were not well examined in the disulfide addition reactions. It was our objectives to find the usefulness of these catalysts in such disulfenylation and to reveal their utilities compared with previous conditions.

We thus surveyed the reaction of $FeCl_3$ first with different substrates. Results with 5 mol% $FeCl_3$ catalyst are summarized in Table 2. In typical runs, $FeCl_3$ was added to a toluene solution of disulfide **2**, followed by addition of alkene **1** at room temperature.[7] After stirring the mixture for the indicated period of time, extractive workup followed by purification through silica gel column chromatography afforded the desired product **5**.

With simple cyclic alkene such as cyclohexene (**1a**), high yield of **6** was attained with diphenyl disulfide (**2a**) (20 h, 98%), while slightly lower yields were observed with dibenzyl disulfide (**2b**) (72 h, 70%) and dimethyl disulfide (**2c**) (20 h, 42%). The $FeCl_3$ catalyst was effective for both cyclic and acyclic alkenes **1a-e**, and afforded desired product **6** in over 90% yield within 26 h (entry

Table 2. $FeCl_3$ catalyzed alkene disulfenylation



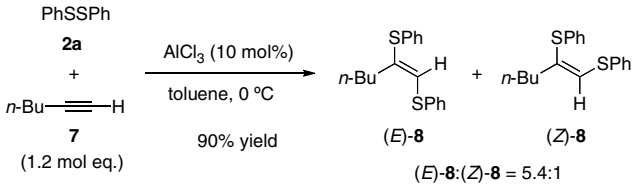
Entry	Alkene	Disulfide	Product	Time (h)	% Yield
1	**1a**	**2a** (R = Ph)	**6aa** (R = Ph)	20	98
2		**2b** (R = Bn)	**6ab** (R = Bn)	72	70
3		**2c** (R = Me)	**6ac** (R = Me)	20	42
4	**1b**	**2a**	**6b**	20	97
5	**1c**	**2a**	**6c**	26	95
6	**1d**	**2a**	**6d**	22	91
7	**1e**	**2a**	**6e**	18	95
8	**1f**	**2a**	**6f**	72	87

4–7 in Table 2). From the terminal alkene **1f**, the desired product **6f** was equally obtained in high yield, while longer reaction time was required (entry 8 in Table 2). Stereochemistry was assigned as a *trans*-addition product, which was explained by the reaction mechanism via S-substituted thiiranium ion intermediate **5**.[8]

There were, however, some problems with the particular substrates. Conjugate alkenes such as styrene or 1,3-cyclohexadiene[9] gave inferior yields, resulting in the complex mixture due to their poor nucleophilicity. Stilbene did not react under the $FeCl_3$ conditions at all. Moreover, alkyne disulfenylation did not proceed under $FeCl_3$ conditions, while with $AlCl_3$, alkyne gave disulfenylation product as an isomeric mixture (mentioned later). Obviously, substrates with polar functionality did not react under these conditions.

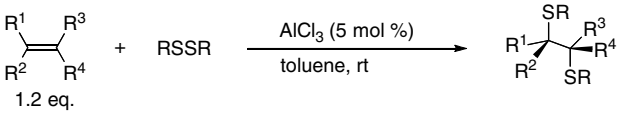
We then turned our attention to $AlCl_3$ catalyst to compare the reactivity in the disufenylation reaction. While $FeCl_3$ catalyzed alkene disulfenylation under mild conditions, $AlCl_3$ could also catalyze same reaction more efficiently in a shorter time as summarized in Table 3.[7] $AlCl_3$ showed thus wider applicability, because of its strong Lewis acidity and usually, good yields were obtained with the substrates which were less reactive (more than 20 h reaction) in the case of $FeCl_3$. It was thus revealed that $AlCl_3$ was more effective than $FeCl_3$ and made the conversion faster than in the case of $FeCl_3$. Cyclic alkenes were most easily converted to the desired products **6** with dialkyl or diaryl disulfides **2**. The terminal alkenes and trisubstituted alkene were converted into corresponding disulfenylation product **6** in high or moderate yields.

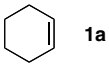
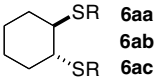
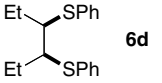
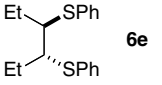
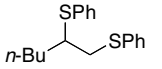
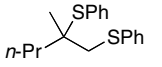
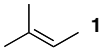
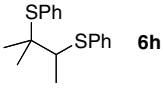
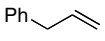
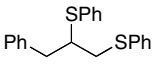
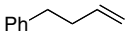
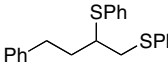
As noted above, with $AlCl_3$, alkyne **7** gave the corresponding disulfenylation product **8** as an isomeric mixture [24 h, (*E*)-**8**/(*Z*)-**8** = 5.4/1] in Scheme 1.[10] We also observed further isomerization of the vinyl disulfide product **8** took place by the influence of $AlCl_3$ present in the reaction mixture.[11] Even though there was a room for improvement in geometric selectivity, it was noteworthy that both alkene- and alkyne-disulfenylation were possible with $AlCl_3$ catalyst, just like $GaCl_3$.[4]

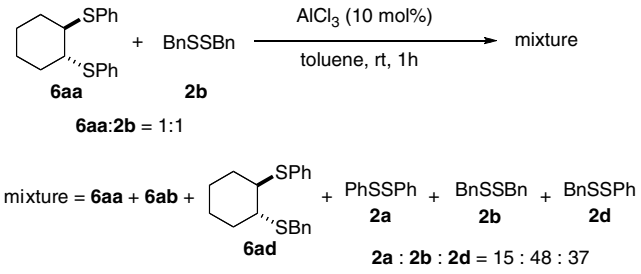


Scheme 1. Disulfenylation of alkyne.

Table 3. $AlCl_3$ catalyzed alkene disulfenylation



Entry	Alkene	Disulfide	Product	Time (h)	% Yield
1	 **1a**	**2a**	 **6aa** **6ab** **6ac**	4	90
2		**2b**		24	82
3		**2c**		24	68
4	 **1d**	**2a**	 **6d**	1	95
5	 **1e**	**2a**	 **6e**	1	98
6	 **1f**	**2a**	 **6f**	12	74
7	 **1g**	**2a**	 **6g**	12	75
8	 **1h**	**2a**	 **6h**	6	57
9	 **1i**	**2a**	 **6i**	24	72
10	 **1j**	**2a**	 **6j**	16	57



Scheme 2. Disulfide scrambling.

Asymmetric version of alkene disulfenylation was a challenging matter, and initial attempt with chiral Lewis acids (such as BINOL complex) was turned to be difficult to achieve in our hands, most probably by the interference with undesired racemization occurred under this reaction conditions (i.e., reversible reaction course; see Fig. 1). Namely, with Lewis acid, 1,2-bis(alkylthio) compound **6** was presumably transformed into *S*-substituted thiiranium ion **5** reversibly, resulting in racemization of the product. Additional experiment as shown in Scheme 2 clearly indicated the reversibility of the disulfenylation reaction and probably a reversible formation of S-substituted thiiranium ion **5** occurred as a key step.

In conclusion, we have disclosed herein a simple procedure for alkene disulfenylation by common Lewis acid catalysts: $FeCl_3$ and $AlCl_3$. Reactions with $FeCl_3$ usually took longer time but almost complete conversion was possible. With $AlCl_3$, reactions were much faster and satisfactory conversions were attained with substrates less reactive towards $FeCl_3$. We thus recommend selecting one of the two common catalysts for a simple and effective alkene disulfenylation. However, because of acidic nature of the reaction mixture, substrates that contain conjugated alkenes and coordinating substituents are not suitable for these catalytic transformations.

Acknowledgments

We thank Prof. M. Shibasaki at Tokyo University for mass spectrum analysis. This work was partially supported by Grant-in-Aid from The Uehara Memorial Foundation. The authors would like to dedicate this paper to Prof. Shibasaki, on the occasion of his 60th birthday.

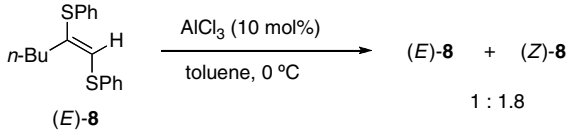
References and notes

1. See for example: De Martino, G.; Edler, M. C.; La Regina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947.
2. Caserio, M. C.; Fisher, C. L.; Kim, J. K. *J. Org. Chem.* **1985**, *50*, 4390.
3. Kitamura, T.; Matsuyuki, J.-I.; Taniguchi, H. *J. Chem. Soc., Perkin Trans.* **1991**, *1*, 1607.
4. Usugi, S. I.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 601.
5. Kondo, T.; Uenoyama, S.; Fujita, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 482.
6. Nishimura, T.; Yoshinaka, Y.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1138.
7. Typical experimental procedures in Tables 2 and 3: to a solution of diphenyldisulfide (**2a**) (2.5 mmol) in toluene (1 mL) was added $FeCl_3$ or $AlCl_3$ (0.125 mmol) and the mixture was stirred at room temperature. Cyclohexene (**1a**) (3.0 mmol) was added to the mixture and resulting mixture was kept stirring around the indicated period. After addition of saturated aqueous $NaHCO_3$ (1 mL), the organic compounds were extracted with ethyl acetate. After removal of solvents, purification with silica-gel column chromatography (hexane only to hexane/ether = 100:1) afforded *trans*-1,2-di(phenylthio)cyclohexane (**6aa**).
   Analytical data for **6aa**,[3] **6ab**,[6] **6ac**,[3] **6b**,[3] **6c**,[3] **6d**,[4] **6e**,[4] **6f** [3] are reported in the literatures.
   2-Methyl-1,2-bis(phenylthio)pentane (**6g**): colorless oil; IR (neat) ν 2958, 2930, 2871, 1583, 1480, 1474, 1438, 1373, 1089, 1025, 750, 738, 704, 693 cm^{-1}; ^1H NMR($CDCl_3$): δ = 7.51 (d, J = 7.5 Hz, 2H), 7.32-7.24 (m, 5H), 7.18 (t, J = 7.5 Hz, 2 H), 7.09 (t, J = 7.5 Hz, 1H), 3.08 (d, J = 12.5 Hz, 1H), 3.05 (d, J = 12.5 Hz, 1H), 1.61–1.37 (m, 4H), 1.24 (s, 3H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 137.54, 137.49, 133.04, 129.30, 128.97, 128.77, 128.58, 125.81, 52.81, 45.46, 41.10, 25.57, 17.54, 14.24; ESI-MS: *m/z* 325 $[M+Na]^+$; HRMS (EI): *m/z* calcd for $C_{18}H_{22}S_2^+$ $[M^+]$: 302.1157; found: 302.1159.
   2-Methyl-2,3-bis(phenylthio)butane (**6h**): colorless oil; IR (neat) ν 2970, 2929, 1583, 1479, 1474, 1437, 1373, 1363, 1112, 1088, 1067, 1024, 749, 705, 693 cm^{-1}; ^1H NMR($CDCl_3$): δ = 7.58–7.56 (m, 2H), 7.40–7.32 (m, 5H), 7.27–7.24 (m, 2H), 7.21–7.17 (m, 1H), 3.31 (q, J = 7.0 Hz, 1H), 1.50 (d, J = 7.0 Hz, 3H), 1.39 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 137.65, 136.51, 131.82, 131.48, 128.99, 128.85, 128.59, 126.55, 53.91, 53.49, 27.92, 25.59, 18.23; ESI-MS: *m/z* 311 $[M+Na]^+$; HRMS (EI): *m/z* calcd for $C_{17}H_{20}S_2^+$ $[M^+]$: 288.1001; found: 288.0998.
   3-Phenyl-1,2-bis(phenylthio)propane (**6i**): colorless oil; IR (neat) ν 1583, 1480, 1438, 1024, 740, 700, 691 cm^{-1};^1H NMR($CDCl_3$): δ = 7.33–7.18 (m, 15H), 3.44–3.38 (m, 1H), 3.29 (dd, J = 14.0, 6.0 Hz, 1H), 3.22 (dd, J = 14.0, 4.5 Hz, 1H), 2.98 (dd, J = 14.0, 9.0 Hz, 1H), 2.93 (dd, J = 14.0, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 138.44, 135.53, 134.08, 132.50, 129.71, 129.39, 128.94, 128.34, 127.29, 126.59, 126.29, 49.75, 38.93, 38.25; ESI-MS: *m/z* 359 $[M+Na]^+$; HRMS (EI): *m/z* calcd for $C_{21}H_{20}S_2^+$ $[M^+]$: 336.1001; found: 336.1009. 4-Phenyl-1,2-bis(phenylthio)butane (**6j**): colorless oil; IR (neat) ν 1584, 1480, 1438, 1025, 739, 699, 692 cm^{-1}; ^1H NMR($CDCl_3$): δ = 7.32–7.30 (t, J = 7.0 Hz, 2H), 7.27–7.19 (m, J = 11H), 7.14–7.10 (m, 2H), 3.27 (dd, J = 14.0, 4.0 Hz, 1H), 3.11 (tt, J = 10.0, 4.0 Hz, 1 H), 2.97 (ddd, J = 14.0, 9.5, 5.5 Hz, 1H), 2.90 (dd, J = 14.0, 10.0 Hz, 1H), 2.43–2.36 (m, 1H), 2.82 (dt, J = 131.5, 8.0 Hz, 1H), 1.90–1.82 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 141.32, 135.32, 134.02, 132.24, 130.51, 128.96, 128.89, 128.55, 128.40, 127.15, 126.48, 125.96, 46.97, 39.85, 33.91, 32.83; ESI-MS: *m/z* 373 $[M+Na]^+$; HRMS (EI): *m/z* calcd for $C_{22}HS_2^+$ $[M^+]$: 350.1157; found: 350.1152.
8. Reaction mechanism of these disulfenylation reactions was well discussed in Refs. 2 and 4.
9. Disulfenylation of 1,3-cyclohexadiene afforded a complex mixture of 1,2- and 1,4-adducts.
10. The *E*/*Z* ratio of **8** was determined from the relative intensity of vinyl proton in NMR spectra;
   (*E*)-1,2-bis(phenylthio)-1-hexene [(*E*)-**8**]: colorless oil; IR (neat) ν 2955, 2928, 1581, 1477, 737, 690 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.41–7.39 (m, 2H), 7.34–7.19 (m, 8H), 6.32 (s, 1H), 2.42 (t, J = 7.5 Hz, 2H), 1.58–1.53 (m, 2H), 1.35

(qt, $J = 7.2$, 7.2 Hz, 2H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 138.39, 136.11, 134.06, 131.49, 129.14, 129.05, 128.60, 127.32, 126.39, 123.90, 32.64, 30.39, 22.26, 13.90$; ESI-MS: m/z 301 $[M+H]^+$.

(Z)-1,2-bis(phenylthio)-1-hexene [(Z)-**8**]: colorless oil; IR (neat) ν 2955, 2928, 1581, 1477, 1439, 740, 690 cm^{-1}; ^1H NMR($CDCl_3$): $\delta = 7.43–7.21$ (m, 10H), 6.56 (s, 1H), 2.25 (t, $J = 7.5$ Hz, 2H), 1.51–1.45 (m, 2H), 1.27–1.23 (m, 2H), 0.83 (t, $J = 7.5$ Hz, 1H);^{13}C NMR ($CDCl_3$): $\delta = 135.90, 134.34, 133.85, 130.49, 129.73, 129.12, 129.09, 128.95, 126.83, 126.73, 36.83, 30.71, 21.93, 13.79$; ESI-MS: m/z 301 $[M+H]^+$.

11. With $AlCl_3$ catalyst, (E)-**8** easily isomerized to (Z)-**8**. The mechanism of isomerization is under investigation.



(*E*)-**8**

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