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N-Ethyldiisopropylamine and Sulfur Dioxide Solutions. 2. Reactions with Conjugate Acceptors

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Solutions of sulfur dioxide and *N*-ethyldiisopropylamine (EDIA) are able to reduce α,β-unsaturated-γ-dicarbonyl compounds (esters or ketones) into α-dicarbonyl alkanes. In contrast, monoactivated Michael acceptors, such as acrylates, give symmetrical sulfones. These processes involve the conjugate addition of HSO_2^-, formed from a charge-transfer complex between EDIA and SO_2. Secondary amines are formed as byproducts. Triethylamine, which forms a more stable complex with sulfur dioxide than EDIA, is far less reactive toward the same substrates.

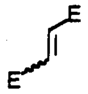
Introduction

Recently, we have shown that the charge-transfer complex between *N*-ethyldiisopropylamine (EDIA) and sulfur dioxide in *N,N*-dimethylacetamide (DMAc) or acetonitrile, leads to the anion-radical of sulfur dioxide and the amine cation-radical. This initially generated $SO_2^{\bullet-}$ abstracts a hydrogen atom from the cation-radical to give the sulfoxylate anion (Scheme 1).[1]

Species such as HSO_2^- and $SO_2^{\bullet-}$ (or $S_2O_4^{2-}$) are reactive towards conjugate acceptors to give reduction[2] or addition products[3] (Scheme 2).

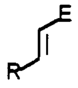
Our first results on the reaction of EDIA and SO_2 solutions with conjugate acceptors have been described in a preliminary report[4] (formation of reduction or addition products). To extend our earlier work, we have investigated the scope of this reaction and propose its mechanism.

Two classes of Michael acceptors were selected for this study which bear either two electron-withdrawing groups (substrates **3**) or only one electron-withdrawing group and another substituent in the 3 position (substrates **4**).



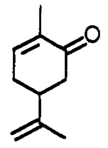
3

a E = CO_2Et (*E*)
b E = CO_2Et (*Z*)
c E = COPh (*E*)
d E = $COCH_3$ (*E*)



4

a E = CO_2Et R = H
b E = CO_2Et R = CH_3
c E = CO_2Et R = Ph
d E = $COCH_3$ R = Ph

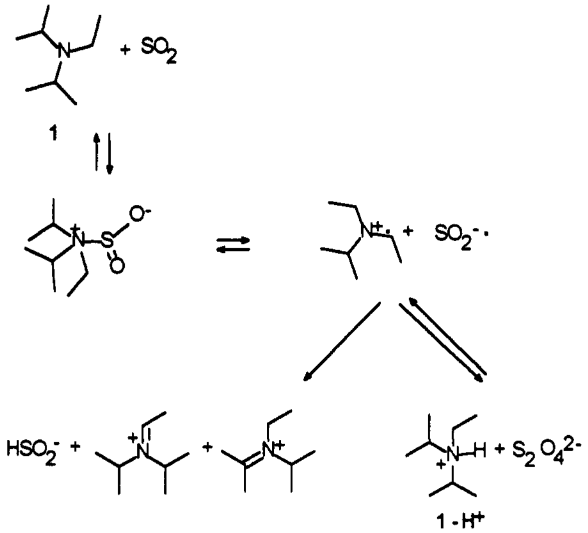


4e

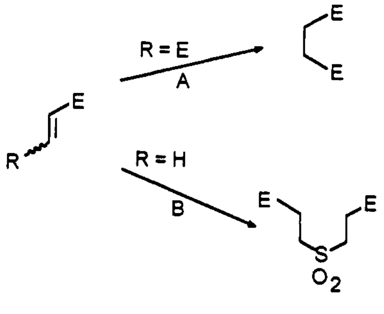
Carvone (**4e**)

In these two classes of alkenes, substituents were chosen in order to modulate either the redox potential[5] (reactivity toward the reducer $SO_2^{\bullet-}$) or the reactivity toward nucleophiles[6] (for example HSO_2^-).

Scheme 1



Scheme 2



Results and Discussion

Alkenes **3** reacted with EDIA and SO_2 to give reduction products (Scheme 2, path A), as reported in Table 1.

Substrates **3a–c** underwent reduction with reaction times longer than the time required for the complete transformation of the EDIA/SO_2 complex into iminium sulfoxylate (45 min).[1] This observation was consistent with a reaction sequence involving HSO_2^-.

In addition, the Et_3N/SO_2 solution (entries 2 and 4) was significantly less reactive than the EDIA/SO_2 complex (entries 1 and 3). Because of the slower transformation of the Et_3N/SO_2 complex than that of the EDIA/SO_2 complex into iminium sulfoxylate, these results also confirm that the sulfoxylate anion is the reactive species.

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[1] Eugene, F.; Langlois, B.; Laurent, E. *New J. Chem.* **1993,** *17,* 815.

[2] Louis-Andre, O.; Gelbard, G. *Bull Soc. Chim. Fr.* **1986,** 565.

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[5] Siegerman, H. In *Techniques of Electroorganic Synthesis*; Weinberg, N. L., Ed.; John Wiley and Sons: New York, 1974; Vol.V, part II, p 720 and 774.

[6] Patai, S.; Rappoport, Z. In *The Chemistry of Alkenes*; Patai, S., Ed.; John Wiley and Sons: London, 1964; Chapt. 8, pp 469–584.

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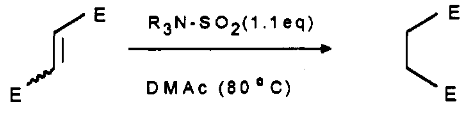
Table 1. Reaction of Alkenes 3 with Tertiary Amine, SO_2 Solutions

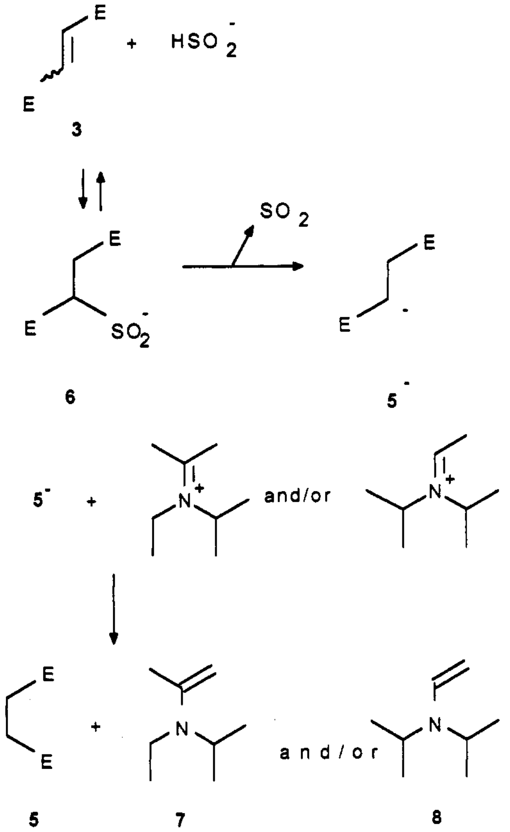


3 a - d 5 a - d

entry	substrates	amine	reaction time (h)	conv (%) 3	yield (%)[a] 5
1	**3a**	EDIA	1.25	100	(65) 58
2	**3a**	Et_3N	23.25	72	(63)
3	**3b**	EDIA	2.50	72	(57)
4	**3b**	Et_3N	23.25	100	(56)
5	**3c**	EDIA	1.25	90	31
6	**3d**	EDIA	0.25	100	43

[a] Isolated yield reported to 100% conversion. NMR yield is shown in parentheses.

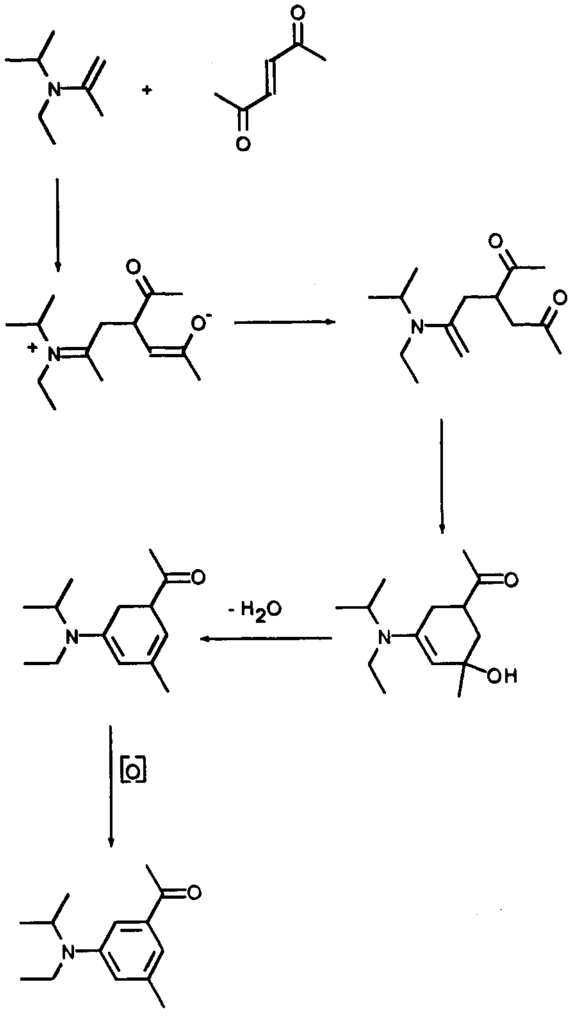
Scheme 3



Hence, the mechanism most consistent with these results is the nucleophilic addition of HSO_2^- to alkenes **3a–c** which leads to the intermediate formation of sulfinate **6** followed by loss of sulfur dioxide and formation of enolate 5^- (which is stabilized by the electron-withdrawing group in the α position). This enolate could be then protonated by iminium cations to give the reduction product (Scheme 3).

3-Hexene-2,5-dione (**3d**) exhibited a greater reactivity than the other substrates: it is known that nucleophilic addition becomes faster when substrates are activated by groups exerting stronger resonating effects.[7] Moreover, the formation of 3-(*N*-ethyldiisopropylamino)-5-methylacetophenone (**9**) in 5% yields seems to us to prove that enamine **7** was present and therefore that HSO_2^- was formed (Scheme 4). Thus, **5d** was formed according to the mechanism described in Scheme 3.

Scheme 4



In contrast to alkenes **3**, alkenes **4** led to sulfones. The results are summarized in Table 2.

Examination of Table 2 shows that substitution in position 3 dramatically decreases the reactivity. Only the terminal alkene **4a** reacted through a 1,4-nucleophilic addition (entry 7). Moreover, the time required for the complete conversion of **4a** (2h) was longer than the time needed for the total transformation of the EDIA, SO_2 solution into iminium sulfoxylate (45 mn).[1] Therefore, the mechanism of sulfone **11a** formation includes, in this case also, an initial 1,4-addition of the sulfoxylate anion HSO_2^- giving the stable sulfinate **12** which adds onto a second molecule of Michael acceptor to lead to sulfone **11a** (Scheme 5).

Products and yields obtained from **4a** and EDIA/SO_2 solutions were similar to those given by the ammonium formate–sulfur dioxide system (known to generate HSO_2^-)[3]: sulfone **11a** was the major product and disulfide **10′a** was isolated as a byproduct. This fact supports our explanation and **10a** and **10′a** could arise from H_2S and sulfur, known to be generated from HSO_2^- in acidic media[8] (Scheme 6).

G. Gelbard and coworkers[9] have shown that the reaction of carvone **4e** with sodium dithionite (generating $SO_2^{\bullet -}$)

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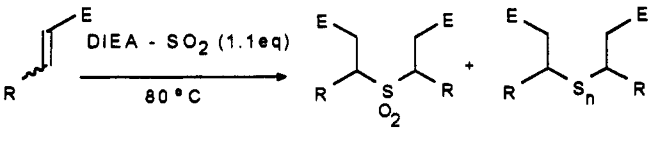
Table 2. Reaction of EDIA, SO_2 Solutions with Alkenes 4a–e



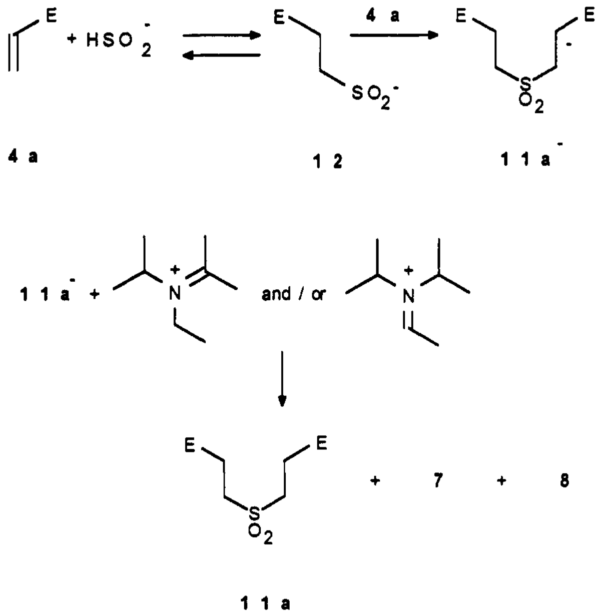
11 a - e   10 a-e (n = 1)

10' a-e (n = 2)

entry	substrates	solvent	reaction time (h)	conv (%) 4	(10 + 10′) yield[a] (%)	11 yield[a] (%)
7	**4a**	DMAc	2	100	9	51
8	**4b**	DMAc	5	20	0	0
9	**4e**	DMAc	5	0	0	0
10	**4c**	CH_3CN	7	0	0	0
11	**4d**	CH_3CN	7	0	0	0

[a] Isolated yield.

Scheme 5



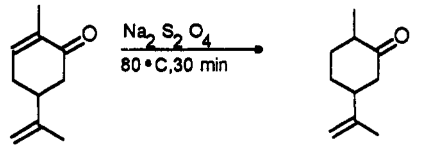
Scheme 6

$$H^+ + 3\,HSO_2^- \longrightarrow H_2S + 2\,HSO_3^-$$

$$H^+ + 2\,HSO_2^- \longrightarrow S + HSO_3^- + H_2O$$

$$H^+ + HSO_2^- + H_2S \longrightarrow 2H_2O + 2\,S$$

Scheme 7

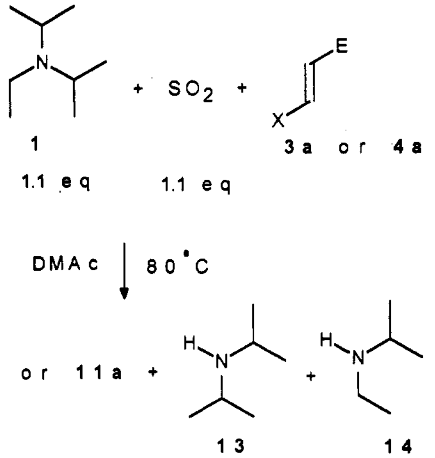


4e

affords dihydrocarvone in 30 min at 80 °C (Scheme 7). However, under our conditions **4e** was unreactive (entry 9).

Thus, the reaction leading to HSO_2^- from $SO_2^{\bullet-}$ (Scheme 1) is faster than the electron transfer between $SO_2^{\bullet-}$ and **4e**. Even in acetonitrile where $SO_2^{\bullet-}$ is generated more rapidly than in DMAc,[1] or when using benzylideneacetone (**4d**), which is more easily reducible (**4e**, $E_{1/2}$ = −1.62 V/SCE; **4d**, $E_{1/2}$ = −1.08 V/SCE),[5] the electron transfer does not occur (entries 10 and 11).

Table 3. Aminated Alkenes Formed after Reaction of EDIA, SO_2 Solutions with 3a and 4a



entry	substrates	reaction time (h)	1/13/14
12	**3a**	47	17/39/44
7	**4a**	2	27/35/38

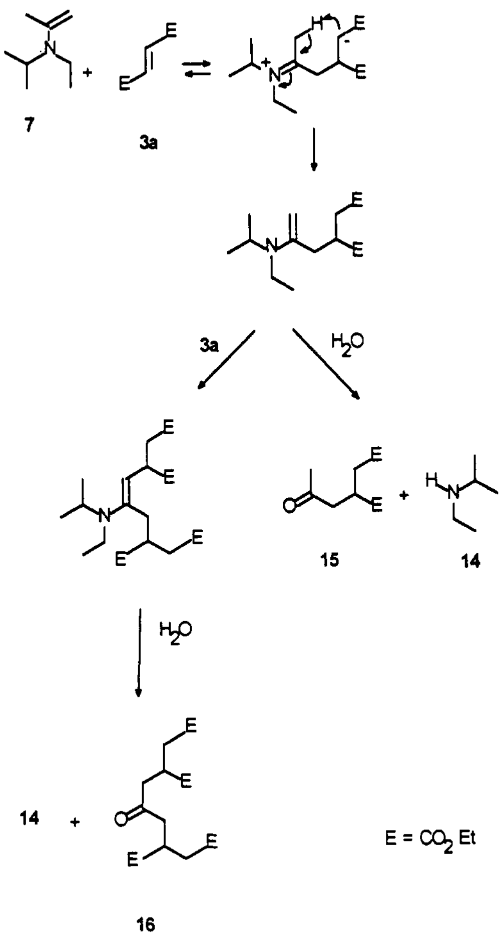
Examination of aminated compounds after workup (Table 3) shows that EDIA mainly afforded an equimolar amount of diisopropylamine and ethylisopropylamine resulting from hydrolysis of enamines **7** and **8** (Table 3). These results are consistent with the mechanisms proposed in Schemes 3 and 5.

In entry 1, formation of enamine **7** was also supported by isolation of small quantities of products **15** (yield 6.2%) and **16** (yield 5.1%). They could be formed by the Michael addition of enamine **7** to **3a** (Scheme 8).

In the case of diesters (or diketones), Scheme 3 shows that SO_2 would not be consumed. Thus, it should be possible to use it in a nonstoichiometric amount. To study this hypothesis, we repeated the reaction with only 1 equiv of EDIA, SO_2 and two of the alkenes. Results are summarized in Scheme 9.

Even with 0.5 equiv of EDIA and SO_2, conversion of **3a** was complete: this result can be only explained by the formation of a new charge-transfer complex between the regenerated sulfur dioxide and enamines **7** and **8**. This new complex would also be able to generate HSO_2^- (Scheme 10).

Scheme 8



Iminium ion **17** would give, after hydrolysis, ethylamine (bp 16–17 °C) and isopropylamine (bp 30–31 °C) which would have been lost during the workup. This would explain the ratios between secondary amines **13** and **14** (14/86).

Conclusion

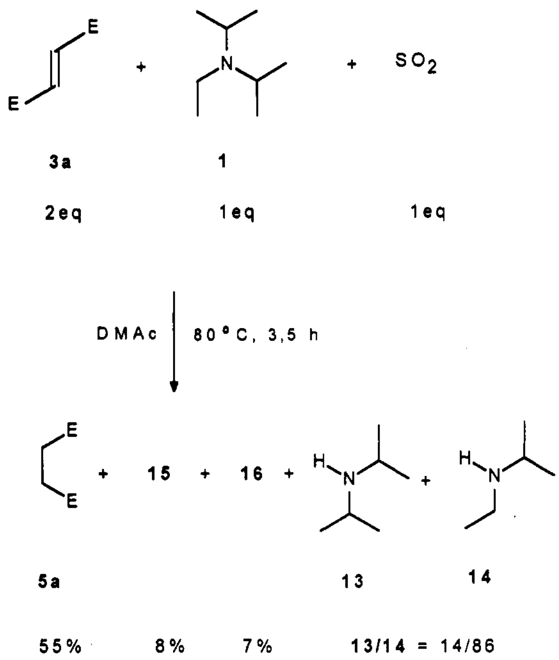
EDIA and SO_2 solutions are reactive toward conjugate acceptors and give either sulfones (with a terminal alkene substituted by one electron-withdrawing group) or reduction products (with alkenes bearing two electron-withdrawing groups).

In all cases, the reactive species is the sulfoxylate anion HSO_2^- generated from a charge-transfer complex between an amine and sulfur dioxide. The amine which presents the best ability to generate HSO_2^- is *N*-ethyldiisopropylamine.

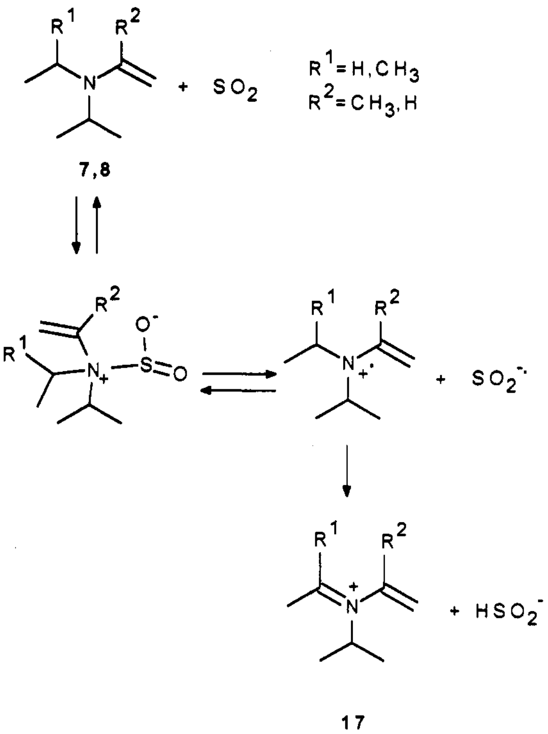
The advantage of these solutions, compared to other systems generating reduced sulfur dioxide species, lies in the possibility of working in homogeneous organic media and in their easy preparation.

This study could be relevant to ecological problems since the growing concentration of sulfur dioxide in the atmosphere raises questions about the biological behavior of this pollutant, mainly toward the aminated systems present in all biological systems. Though interactions between sulfur dioxide and some simple tertiary amines, such as trimethylamine[10] or *N*-benzyl-1,4-dihydronicotinamide[11] have been reported, little is known about the reactivity of branched tertiary amines, such as *N*-ethyldiisopropylamine, toward SO_2 and the behavior of the resulting complexes in enzymatic systems.

Scheme 9



Scheme 10



Experimental Section

General. ^1H NMR spectra of amine hydrochlorides were recorded in DMSO-d_6 on a Bruker AM 300 apparatus; the others were carried out in $CDCl_3$ on a Varian EM 360 (or 360 L), a Bruker AM 300, or a Bruker AC 200 spectrometer. They were carried out at 60 MHz unless otherwise indicated. Chemical shifts are given in ppm relative to TMS (0.00 ppm).

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^{13}C NMR spectra were recorded on a Bruker AC 200 or on a Bruker AM 300 apparatus. The mass spectra were recorded on a Nermag R10–105 spectrograph (electron impact at 70eV) either with direct introduction or after mass-chromatography coupling. Elemental analyses were performed by the CNRS Analysis Center at Vernaison. Samples were routinely examined by gas chromatography on a Varian 3300 apparatus (Megabore column: 15 m × 0.25 mm, detector: catharometer) with an internal standard. Flash chromatography was performed on Merck 60H silica gel with ether/petroleum ether or methylene chloride/petroleum ether mixtures as eluents.

Acetonitrile (SDS-Chromasol) was kept on 3-Å molecular sieve. *N,N*-dimethylacetamide (DMAC) (Aldrich-GC) was distilled under atmospheric pressure (bp 168 °C) and dried on 4-Å molecular sieve for 24 h. 3-Hexene-2,5-dione was prepared according to literature procedures.[12] Other starting materials were commercially available and used without purification.

Preparation ot the Amine/SO_2 Solutions. See reference 1 for experimental details.

General Procedure for Reactions of Amine/SO_2 Solutions and Alkenes. To a solution of EDIA and SO_2 in DMAc or acetonitrile was added the alkene in the same solvent. The mixture was allowed to warm up for a variable time at 80 °C. The mixture was then acidified with 40 mL of a 10% H_2SO_4 solution, extracted with diethyl ether (3 × 25mL) or CH_2Cl_2 (3 × 25mL), washed with water, and dried over $MgSO_4$.

The solvent was removed on a rotary evaporator leaving a yellow oil. The composition of the crude product was determined by NMR spectroscopy (intensity standard $PhCF_3$) or gas chromatography. This crude product was purified by flash column chromatography.

Yields were calculated with respect to reacted alkenes.

Reduction of Alkenes 3. Entry 1: EDIA (1.70 g, 13.2 mmol), SO_2 (0.84 g, 13.1 mmol), ethyl fumarate **3a** (2.14 g, 12.44 mmol) in DMAc (13 mL); 80 °C for 75 min. The crude product (2.20 g) analyzed by ^{1}H NMR contained ethyl succinate (**5a**) (1.4 g, 8.05 mmol, 65%). It was purified by flash chromatography (eluent: ether–petroleum ether) to give **5a** (1.25 g, 7.18 mmol, 58%), **15** (180 mg, 0.78 mmol, 6.2%), and **16** (250 mg, 0.62 mmol, 10%).

15: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 3H, ^3J = 7.3 Hz), 1.26 (t, 3H, ^3J = 7.3 Hz), 2.18 (s, 3H), 2.54–2.78 (m, 3H), 2 92–3.01 (m, 1H), 3.26 (quintuplet, 1H, ^3J = 6.5 Hz), 4.14 (q, 2H, ^3J = 7.3 Hz), 4.15 (q, 2H, ^3J = 7.3 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.05, 14.15, 30.04, 35.36, 36.47, 43.97, 60.71, 61.00, 171.29, 173.58, 206.05; MS *m/z* (rel intensity) 231 (M^+ + 1, 1.12), 215 (1.38), 185 (23), 156 (9.6), 141 (19), 97 (13.6), 73 (9.1), 55 (12.7), 43 (100), 29 (51.9); CI-MS 231 (100, $[M + H]^+$).

16: Mixture ot two diastereoisomers **16a** and **16b** (ratio 40/60). **16a**: δ ^{1}H NMR (300 MHz, $CDCl_3$) 1.24 (t, 12H, ^3J = 7 Hz), 2.5–2.72 (m, 6H), 2.93, (dd, 2H, ^2J = 6.9 Hz, ^3J = 3.4 Hz), 3.24 (m, 2H), 4.11 (q, 8H, ^3J = 7 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.10, 14.35, 35.29, 36.47, 43.27, 60.73, 61.07, 171.48, 173.48, 205.77. **16b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, 12H, ^3J = 7.3 Hz), 2.5–2.72 (m, 6H), 2.97 (dd, 2H, ^2J = 6.9 Hz, ^3J = 3.4 Hz), 3.24 (m, 2H) 4.11 (q, 8H, ^3J = 7.3 Hz); ^{13}C NMR (75,4 MHz, $CDCl_3$) δ 14.20, 14.35, 35.42, 36.47, 43.27, 60.73, 61.07, 171.55, 173.48, 205.77; MS *m/z* (rel intensity) 357 (M^+ − 45, 3.49), 311 (10.2), 283 (12.0), 215 (100), 187 (41.9), 159 (24.5), 141 (75.7), 113 (25.9), 99 (19.1), 85 (17.0), 55 (22.4), 41 (27.7). CI-MS 403 (100 , $[M + H]^+$). Anal. Calcd for $C_{19}H_{30}O_9$: C, 56.70; H, 7.51. Found: C, 56.87; H, 7.56.

Entry 2: Et_3N (1.15 g, 11.4 mmol), SO_2 (0.77 g, 12.05 mmol), **3a** (1.83 g, 10.64 mmol), DMAc (20 mL); 80 °C for 75 min. The crude product (1.67 g) yields (^{1}H NMR) **3a** (0.50 g, 2.91 mmol, 28%) and **5a** (0.84 g, 4.83 mmol, yield 63%).

Entry 3: EDIA (0.69 g, 5.35 mmol), SO_2 (0.36 g, 5.6 mmol), ethyl maleate (**3b**) (0.86 g, 5.0 mmol), DMAc (10.6 mL); 80 °C for 2 h, 30 min. The crude product (0.98 g) yields (^{1}H NMR) **3b** (0.25 g, 1.45 mmol, 28%) and **5a** (0.35 g, 2.01 mmol, yield 57%).

Entry 4: Et_3N (1.01 g, 9.9 mmol), SO_2 (0.65 g, 10.1 mmol), **3b** (1.50 g, 8.7 mmol), DMAc (21 mL); 80 °C for 23 h, 15 min. The crude product (1.43 g) yield (^{1}H NMR): **5a** (0.85 g, 4.89 mmol, 56%).

Entry 5: EDIA (1.40 g, 10.85 mmol), SO_2 (0.68 g, 10.7 mmol),*trans*-dibenzoylethylene (**3c**) (2.44 g, 10.3 mmol), DMAc (19 mL); 80 °C for 75 min. After extraction with methylene chloride, purification of the crude product (4.80 g) gave (eluent: methylene chloride–petroleum ether) dibenzoylethane (**5c**) (0.76 g, 3.19 mmol, yield 31%).

Entry 6: EDIA (1.18 g, 9.13 mmol), SO_2 (0.57 g, 8.84 mmol), *trans*-3-hexene-2,5-dione (**3d**) (0.94 g, 8.4 mmol), DMAc (17 mL); 80 °C for 15 min. After extraction with methylene chloride, purification of the crude product (4.80 g) gave (eluent: methylene chloride–petroleum ether) **9** (80 mg, 0.37 mmol, 10%), 2,5-hexanedione (**5d**) (0.41 g, 1.72 mmol, 43%). **9**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.15 (t, 3H, ^3J = 7 Hz), 1.2 (d, 6H, ^3J = 7 Hz), 2.35 (s, 3H), 2.55 (s, 3H), 3.25 (q, 2H, ^3J = 7 Hz), 4.1 (septuplet, 1H, ^3J = 7 Hz), 6.7–7.3 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.83, 20.09, 21.95 (2C), 26.81, 37.87, 48.45, 109.35, 117.26, 118.18, 138.18, 138.99, 148.63, 199.19; MS *m/z* (rel intensity) 219 (M^+ , 20.76), 204 (100), 162 (15.7), 134 (12.6), 43 (38.1).

Entry 12: EDIA (1.23 g, 9.55 mmol), SO_2 (0.67 g, 9.59 mmol), ethyl fumarate **3a** (1.63 g, 9.50 mmol), DMAC (20 mL); 80 °C for 1 h, 40 min. The extraction of aminated alkenes from the aqueous layer gave a white solid (1.45 g), containing EDIA hydrochoride, diisopropylamine hydrochloride, and ethylisopropylamine hydrochloride (17/39/44).

Entry 13: EDIA (1.66 g, 12.87 mmol), SO_2 (0.83 g, 12.96 mmol), **3a** (4.42 g, 25.72 mmol), DMAc (25 mL); 80 °C for 3 h, 30 min. Purification of the crude product (4.44 g) gave (eluent: ether–petroleum ether) **5a** (2.5 g, 14.37 mmol, 56%), **15** (0.47 g, 2.04 mmol, 16%), **16** (0.73 g, 1.82 mmol, 14%). The extraction of aminated alkenes from the aqueous layer gave a white solid (1.52 g) containing diisopropylamine hydrochloride and ethylisopropylamine hydrochloride in the ratio 14/86.

Sulfonylation of Alkenes 4. Entry 7: EDIA (2.26 g, 17.54 mmol), SO_2 (1.12 g, 17.53 mmol), ethyl acrylate (**4a**) (1.64 g, 16.34 mmol), DMAc (32 mL); 80 °C for 2 h. After extraction with methylene chloride, purification of the crude product (2.54 g) gave (eluent: methylene chloride–petroleum ether) **10a** + **10′a** (0.19 g, 9%) and **11a** (1.15 g, 4.32 mmol, 53%). Sulfide **10a** and disulfide **10′a** were obtained as a mixture and identified by mass-chromatography coupling. **10a**: MS *m/z* (rel intensity) 234 (M^+, 12.34), 188 (24.26), 161 (17.96), 143 (10.62), 115 (34.72), 102 (65.75), 87 (38.83), 74 (42.89), 73 (64.03), 55 (36.28), 45 (36.39), 29 (100). **10′a**: MS *m/z* (rel intensity) 266 (M^+, 22.02), 221 (13.48), 132 (30.27), 73 (30.46), 59 (19.03), 55 (49.73), 45 (12.21), 29 (100). Sulfone **11a** was identified by its NMR spectrum ($CDCl_3$) identical with that previously reported.[3] The extraction of aminated product (see reference 1 for experimental details) from the aqueous layer gave a white solid (1.66g) composed of EDIA hydrochloride, diisopropylamine hydrochloride, and ethylisopropylamine hydrochloride in the ratio 27/35/38.

Entry 8: EDIA (1.18 g, 9.13 mmol), SO_2 (0.60 g, 9.45 mmol), ethyl crotonate (**4b**) (0.97 g, 8.48 mmol), DMAc (22 mL); 80 °C for 5 h. The reaction mixture was extracted with diethyl ether; then, the organic layer was concentrated under atmospheric pressure ($\theta < 55$ °C) and analyzed by gas chromatography (internal standard: decane): ethyl crotonate (**4b**) (0.78 g, 6.84 mmol, 80.7%).

Entry 9: EDIA (1.04 g, 8.0 mmol), SO_2 (0.55 g, 8.5 mmol), (−)-carvone (**4e**) (0.96 g, 6.4 mmol), DMAc (10 mL); 80 °C for 5 h. Analysis by gas chromatography and ^{1}H NMR of the crude product (1.14 g) showed that **4e** was unchanged.

Entry 10: EDIA (0.89 g, 7.75 mmol), SO_2 (0.69 g, 10.8 mmol), ethyl cinnamate (**4c**) (1.03 g, 5.83 mmol), CH_3CN (10 mL); 80 °C for 7 h. The crude product (1.07 g) was analyzed by ^{1}H NMR and gas chromatography: **4c** (1.00 g, 5.82 mmol, 100%) was recovered.

Entry 11: EDIA (1.78 g, 13.8 mmol), SO_2 (0.93 g, 14.5 mmol), benzylidene acetone (**4d**) (1.31 g, 9.0 mmol), CH_3CN (15 mL); 80 °C for 7 h. Analysis of the crude product (1.53 g) by ^{1}H NMR and gas chromatography gave **4d** (1.30 g, 9.0 mmol, 100%).

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