Stereoselectivity Control in Reactions of Tertiary 2-Oxacycloalkyl Radicals

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Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday, for his formidable and communicative enthusiasm for chemistry

The stereochemical outcome of reactions mediated by tertiary 1,3-dioxolan-4-yl and oxiranyl cyclic radicals has been investigated. The presence of a very bulky substituent next to the radical center has a remarkable *syn* directing effect. These stereoselectivities are rationalized by a model which takes into account radical pyramidalization, steric interactions between the substituents attached to the cycle and steric interactions with the incoming radical trap.

The stereoselectivity of free radical reactions is a field of intense research. Considerable progress has been achieved and is summarized in recent comprehensive reviews.[1] 1,2-Asymmetric induction in cyclic radicals represents one of the most straightforward cases to examine. A simple rule has been proposed by Giese to account for the stereoselectivity in such systems: the preferred reaction occurs *anti* to the substituent adjacent to the radical center.[1c] As a corollary, the *anti* selectivity is enhanced as the bulk of the adjacent substituent increases. This rule is general and valid for every cycle size. Some limitations are known, for instance with σ-radicals such as substituted cyclopropyl radicals, the rate of inversion has to be faster than the radical reaction. Other factors such as the nature of the radical trap, stereoelectronic effects and torsional effects (in case of 6-membered ring) also influence the stereochemical outcome of the reaction.[2] Few exceptions to this rule have been observed. Cases involving nitrogen substituted radicals have been reported where the amide or carbamate protective groups as well as pyramidalization of the nitrogen atom play an important role.[3] Complete *syn* selectivity has been observed in polycyclic tertiary amidyl radicals, in these cases, the stereoselectivity correlates with product stability.[4] Carbonyl stabilized radicals bearing an exocyclic substituent at the radical center of type CH_2R are reduced *syn* to the β-substituent.[5] This is rationalized by the presence of allylic 1,3-strain which forces the R moiety to occupy a position *anti* to the β-substituent and preferential attack occurs *anti* to the exocyclic R group and *syn* to the β-substituent. Entropic effects also play a role, particularly at elevated temperature.[5d] Several examples of *syn* reactions involving radicals,[6] anomeric pyranosyl radicals[7] and cyclic sulfoxides[8] have also been reported and are attributed to stereoelectronic effects. Recently, during our study of the reactions of 1,2-dialkyl-1,2-dioxy-substituted radicals, we have found an intriguing exception. Under chelation control conditions, the reduction of radical **1r** occurs preferentially *syn* to the large neighboring substituent (Figure 1).[9] This exception to Giese's rule is best explained by a pyramidalized transition state in which steric interactions between the substituents at C(1) and C(2) force the reaction to occur preferentially *syn* to the large substituent. Such an effect is expected to be of importance for any kind of cyclic 1,2-disubstituted radicals.

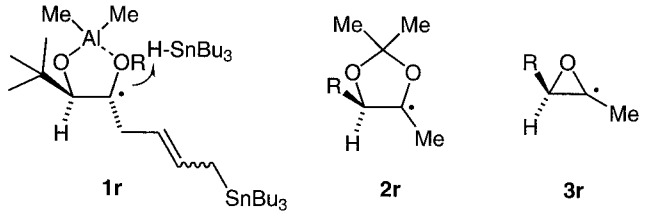
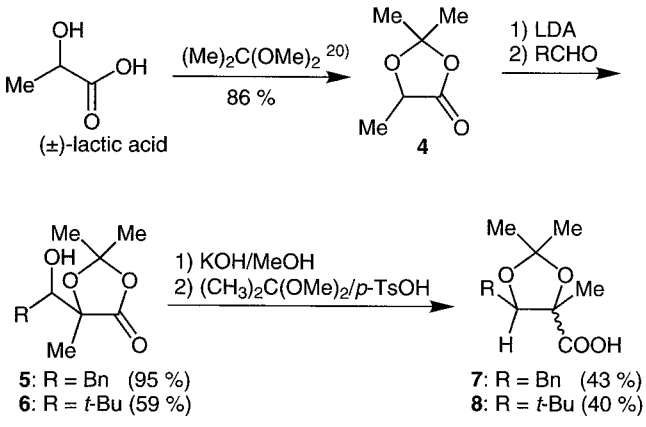


Figure 1

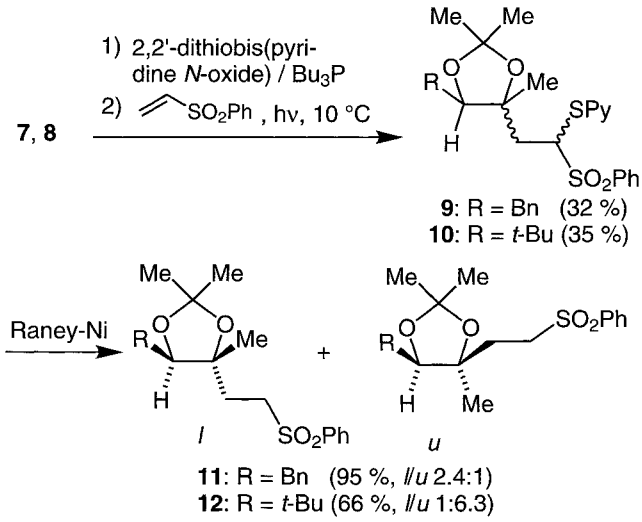
In this paper, we wish to report two cases of tertiary cyclic radicals and to discuss the different factors governing the stereoselectivity. Dioxolanyl radicals of type **2r** and oxiranyl radicals **3r** were chosen for this first investigation (Figure 1). Our results will allow Giese's rule for cyclic radicals to be refined by taking into account radical pyramidalization in the transition state, steric effects between the substituents attached to the cycle and the nature of the radical trap.

a) Dioxolanyl radicals of type **2r**. These radicals are analogous to the 5-membered chelate intermediate **1r**, therefore we expect a very similar behavior for the stereochemistry of their reactions.[10] The precursors **7** and **8** were prepared in four steps from (±)-lactic acid according to Scheme 1. Acetalization of (±)-lactic acid gave the dioxolanone **4** (86%) which was condensed with phenylacetaldehyde and pivalaldehyde to afford the alcohols **5** (95%) and **6** (59%) respectively. Saponification with KOH in MeOH followed by treatment with 2,2-dimethoxypropane/*p*-TsOH afforded the acids **7** (43%, one diastereoisomer) and **8** (40%, mixture of diastereoisomers).



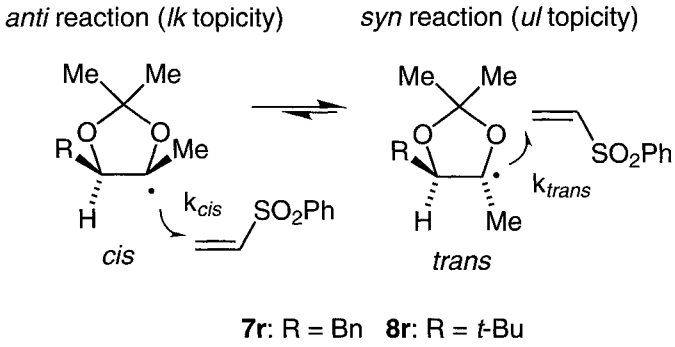
Scheme 1

The α-oxy radicals were generated from **7** and **8** via the corresponding Barton esters (Scheme 2). Due to their instability, these esters were prepared in situ by mixing the carboxylic acid in dichloromethane with 2,2'-dithiodipyridine 1,1'-dioxide and tributylphosphine at 10 °C.[11] An excess of phenyl vinyl sulfone and Bu_3SnH were added and the reaction mixture was irradiated with a 300 W sun lamp at 10 °C to give **9** (32%) and **10** (35%), respectively. The ratio of diastereoisomers could not be determined with precision at this point due to the presence of a 1:1 mixture of epimers resulting from the *S*-pyridyl trapping reaction. Desulfurization using Raney nickel gave **11** and **12** which were analyzed for their diastereoisomer contents. The formation of **11** was slightly stereoselective in favor of the *like* isomer (*l*/*u* 71:29). By increasing the size of the neighboring group (R = *t*-Bu), the sense of the stereoselectivity was inverted and *u*-**12** was isolated as the major isomer (*l*/*u* 14:86). In this particular case, the intermediate radical is trapped by the vinyl sulfone in a *syn* process relative to the very bulky *tert*-butyl group.[12]



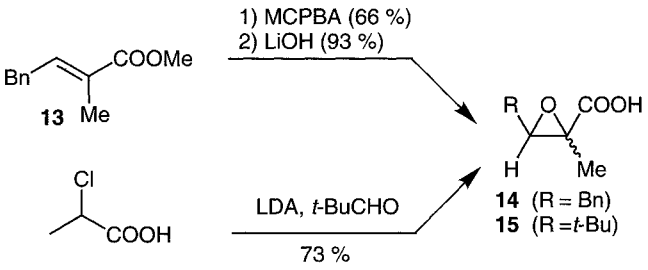
Scheme 2

These results parallel the one we have obtained in chelation controlled reactions. A similar rationalization can be proposed: the pyramidalized[13] radical intermediates **7r** and **8r** lead to two different transition states, namely the *anti* reaction transition state (*lk* topicity) and the *syn* reaction transition state (*ul* topicity) (Scheme 3). The *anti* reaction corresponds to the classical Giese's model, this situation is disfavored by steric interactions between the R group and the vicinal *cis* methyl group and favored by the fact that the reaction is occurring *anti* to the substituent R. The situation is completely inversed with the *syn* reaction: the *syn* attack is disfavored by steric interactions between R and the radical trap and favored by the *trans* arrangement of the two vicinal substituents of the dioxolane ring. The stereochemistry is then governed by a delicate balance between the size of the substituent R and the size of the radical trap. With the bulky *tert*-butyl group, this leads to an inversion of selectivity relative to Giese's model. This can also be described as a Curtin–Hammett situation where the two radical conformers *cis* and *trans* are in rapid equilibrium,[14] the second one being more stable due to the *trans* arrangement of the substituents. However, the rate constant for the radical addition onto the vinyl sulfone is smaller for the *trans* conformer than for the *cis* one ($k_{trans} < k_{cis}$). With small R groups (**7r**), the relative rate constants dominates and the major product is issued by reaction of the less stable *cis* conformer (Giese's model), with bulky R groups (**8r**), the equilibrium is fully displaced in favor of the *trans* conformer so that the equilibrium factor dominates the difference of reaction rates.[15,16]



Scheme 3

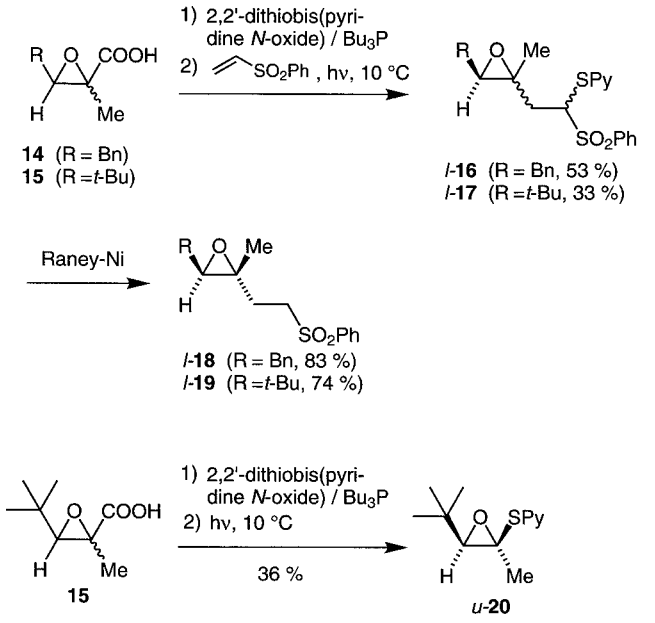
b) Oxiranyl radicals of type **3r**. A situation similar to the dioxolanyl radicals examined above was expected for these radicals. However, the particular nature of the 3-membered ring was expected to bring a new insight into the reaction of cyclic oxygen substituted radicals.[17] The carboxylic acids **14** and **15** are suitable radical precursors for our study. Compound **14** was prepared by epoxidation of the corresponding unsaturated ester **13** and saponification. On the other hand, a Darzens condensation between 2-chloropropionic acid and pivalaldehyde gave the precursor **15** (Scheme 4).



Scheme 4

The oxiranyl radicals were generated from the carboxylic acids via in situ formation of the Barton esters. In the presence of phenyl vinyl sulfone, only the *like* configurated diastereoisomers **18** and **19** were formed after desulfurization starting either from **14** and **15** (Scheme 5).[12,18] No inversion of selectivity was observed with the *tert*-butyl substituent. The influence of the radical trap was investigated next. Unfortunately, the simple reduction reactions with Bu_3SnH gave no reproducible results. Surprisingly, irradiation of the Barton ester prepared from **15** furnished the rearranged product **20** as a single *unlike* diastereoisomer in 36% yield.[19] This complete stereoselectivity should however be considered with

care because of the low yield of this reaction. Indeed, the second diastereoisomer *l*-**20** was not observed even in traces suggesting that some decomposition may have occurred. Moreover, irradiation of the Barton ester derived from **14** gave no stable products.



Scheme 5

From our results, it appears that 1,2-disubstituted oxiranyl radicals **14r** and **15r** behave quite differently to dioxolanyl radicals. They react with alkenes such as vinyl sulfones according to Giese's model. In this particular case, steric interactions between the alkene moiety and the R substituent dominate the interactions between the R and the methyl group at cyclopropane in the transition states whatever the size of the R group. The particular geometry of the 3-membered ring generates a strong shielding of the face *syn* to the R group (R = benzyl or *tert*-butyl) so that only the *anti* reaction (*lk* topicity) occurs with an olefinic radical trap. However, the *syn* attack (*ul* topicity) is preferred (or at least occurs) when radical **15r** reacts with the pyridinethione derivative. This may result from the length of the forming C–S bond in the transition state. This situation renders the steric interactions between the pyridinethione and the adjacent *tert*-butyl group much less important than in the case of the vinyl sulfone. Interpretation of the results based on Curtin–Hammett principle is also possible and leads to the same conclusions (see discussion of the dioxolanyl radical, vide supra).

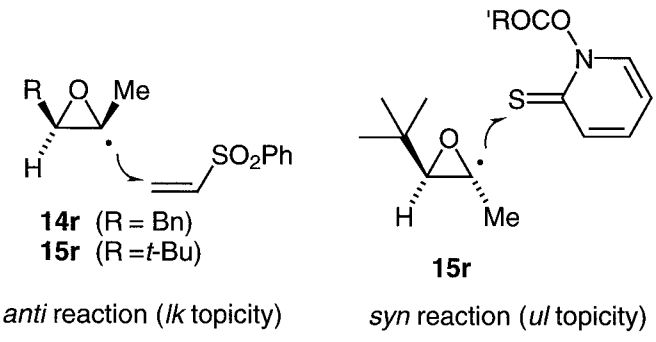


Figure 2

To conclude, in 1,2-disubstituted cyclic radicals, several factors have to be considered in order to understand and predict correctly the stereochemical outcome, and simple application of Giese's rule to these radicals is not possible. The first important factor is steric interactions between the substituents at the stereogenic center and the incoming radical trap. These factors strongly depend on the size of the radical and the length of the bond in formation in the transition state. The second contribution is steric interactions between the vicinal substituents attached to the cycle, these interactions are particularly important in the transition state due to pyramidalization of the radical center. Other factors pointed out by Giese are of course still valuable with these radicals and should also be considered. These results are of importance since 1,2-disubstituted cyclic radicals are particularly suitable for the stereoselective elaboration of quaternary carbon centers. Experiments with different types of cycloalkyl radicals as well as transition state calculations are actually underway in our laboratory in order to get a more complete understanding of the situation.

Irradiations were performed using a sun lamp Osram Ultra-Vitalux 300 W. Mps using a Büchi Tottoli apparatus were not corrected;. IR: Perkin-Elmer 16PC and Mattson Unicam 5000; in cm^{-1}. NMR: Varian Gemini 200 (^1H 200 MHz and ^{13}C 50.3 MHz) if not specified or Bruker AM 360 (^1H 360 MHz); for ^1H in ppm relative to $CDCl_3$ (–7.26 ppm), for ^{13}C in ppm relative to $CDCl_3$ (–77.0 ppm); unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$; ^{13}C multiplicities were determined by the APT sequence; coupling constants *J* are given in Hz. MS: Vacuum Generators Micromass VG 70/70E DS 11-250; EI (70 eV), CI (NH_3 gas); *m/z* (%). Elemental Analysis: Ilse Beetz, Microanalytisches Laboratorium, D-8640 Kronach, Germany and Ciba-Geigy Mikrolabor, Marly, Switzerland.

General Procedure 1:
A cooled (–100 °C) solution of **4** (23.1 mmol) in THF (67 mL) was added to 1 M LDA (24.2 mmol) generated in situ at –78 °C by addition of BuLi (1.6 M/hexane, 24.2 mmol) to diisopropylamine (24.2 mmol) in THF (6.0 mL). After 45 min, the aldehyde (34.6 mmol) was added at –78 °C and the solution left for 4 h at this temperature. The reaction was quenched at –78 °C by adding HOAc (2 mL) in THF (10 mL). The temperature was allowed to rise to r.t. and poured into H_2O (300 mL). The aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by FC.

General Procedure 2:
KOH (44.8 mmol) was added slowly to the disubstituted 1,3-dioxolan-4-one (11.2 mmol) in MeOH (25 mL). The resulting mixture was stirred for 2 h at r.t. and then acidified to pH 2 with 10 % aq H_2SO_4. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the carboxylic acid. Then 2,2-dimethoxypropane (4.76 mmol) and *p*-TsOH (4.65 mmol) were added at r.t. to a solution of the carboxylic acid (0.47 mmol) in anhyd DMF (10 mL). The resulting solution was left overnight, diluted with Et_2O (100 mL), treated with 10 % aq NaOH (20 mL) and washed with H_2O (30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The product was used without further purification in the next step.

General Procedure 3:
Tributylphosphine (2.40 mmol) was added under N_2 at 0 °C to a solution of the carboxylic acid (1.83 mmol) and 2,2'-dithiobis(py-

ridine *N*-oxide) (2.40 mmol) in CH_2Cl_2 (6.5 mL). The mixture was stirred at 0 °C in the dark (the reaction flask was covered with aluminum foil) for 2 h. Phenyl vinyl sulfone (5.49 mmol) in CH_2Cl_2 (30.5 mL) was added and the yellow solution irradiated with a sun lamp (300 W) at 10 °C for 4 h. The solvent was evaporated and the crude product was purified by FC.

General Procedure 4:
Raney nickel (1.00 g) was added to a solution of the pyridyl derivative (0.50 mmol) in absolute EtOH (2.5 mL) and the mixture was heated under reflux for 6 h. The suspension was filtered through Celite and the solvent evaporated. The crude product was purified by FC.

(±)-2,2,5-Trimethyl-1,3-dioxolan-4-one (4):[20]
A solution of (±)-lactic acid (14.4 g, 0.21 mol) and 2,2-dimethoxypropane (26.4 mL, 0.21 mol) in benzene (170 mL) was heated under reflux for 3 h while distilling MeOH in a Dean–Stark apparatus. The resulting solution was concentrated under reduced pressure to afford **4** (17.9 g, 86%) as a colorless liquid.

^{1}H NMR: δ = 4.41 (q, J = 6.8 Hz, OCH), 1.54 (s, Me), 1.47 (s, Me), 1.40 (d, J = 6.8 Hz, MeC*H*).

^{13}C NMR: δ = 173.58 (s), 110.09 (s), 70.19 (d), 27.20 (q), 25.35 (q), 17.14 (q).

5-(1-Hydroxy-2-phenylethyl)-2,2,5-trimethyl-1,3-dioxolan-4-one (5):
According to General Procedure 1, compound **4** (3.00 g, 23.1 mmol) and phenylacetaldehyde (4.5 mL, 34.6 mmol) followed by FC (Et_2O/hexane 1:3) of the crude product gave **5** (5.47 g, 95%, mixture of diastereoisomers) as a colorless liquid.

Diastereoisomer 1:
^{1}H NMR: δ = 7.48–7.05 (m, 5 arom. H), 3.96 (dd, J = 10.8, 2.5 Hz, C*H*OH), 3.04 (dd, J = 13.9, 2.4 Hz, PhC*H*H), 2.68 (dd, J = 13.9, 10.5 Hz, PhCH*H*), 1.95 (s (br), OH), 1.68 (s, Me), 1.64 (s, Me), 1.52 (s, Me).

^{13}C NMR: δ = 174.14 (s), 137.64 (s), 129.33 (d), 128.68 (d), 126.75 (d), 110.45 (s), 82.90 (s), 74.90 (d), 36.74 (t), 28.98 (q), 27.53 (q), 21.31 (q).

Diastereoisomer 2:
^{1}H NMR: δ = 7.45–7.10 (m, 5 arom. H), 3.94–3.81 (m, CHOH), 2.95–2.80 (m, $PhCH_2$), 2.28 (d, J = 3.7 Hz, OH), 1.65 (s, Me), 1.60 (s, Me).

^{13}C NMR: δ = 174.01 (s), 138.03 (s), 129.29 (d), 128.53 (d), 126.62 (d), 110.26 (s), 81.85 (s), 76.16 (d), 37.35 (t), 28.77 (q), 27.72 (q), 20.69 (q).

Mixture of diastereoisomers:
IR (film): ν = 3504 (s, br), 2992 (m), 2939 (m, br), 1787 (s), 1378 (s), 1286 (s, br), 1128 (s), 1082 (s) cm^{-1}.

EIMS: m/z (%) = 251 (4, M^+), 130 (79), 91 (67), 59 (100), 43 (97).

Anal. Calcd for $C_{14}H_{18}O_2$: C, 67.18; H, 7.25. Found: C, 67.23; H, 7.14.

5-(1-Hydroxy-2,2-dimethylpropyl)-2,2,5-trimethyl-1,3-dioxolan-4-one (6):
According to General Procedure 1, from compound **4** (6.20 g, 47.6 mmol) and pivalaldehyde (8.1 mL, 71.4 mmol). The temperature was allowed to rise to −20 °C, after 3 h the mixture was treated with 10% aq NH_4Cl (450 mL). FC (Et_2O/hexane 1:3) of the crude product gave **6** (6.09 g, 59%, mixture of diastereoisomers) as a colorless liquid.

IR (film): ν = 3257 (m, br), 1778 (s) cm^{-1}.

^{1}H NMR: δ = 3.51 (d, J = 7.8 Hz, C*H*OH, diast. 1), 3.41 (d, J = 3.7 Hz, C*H*OH, diast. 2), 3.02 (d, J = 3.7 Hz, OH, diast. 2), 2.20 (d, J = 7.8 Hz, OH, diast. 1), 1.80–1.48 (m, 2 Me), 1.06 (s, *t*-Bu).

^{13}C NMR: δ = 176.36 (s, diast. 1), 175.45 (s, diast. 2), 110.37 (s, diast. 1), 110.22 (s, diast. 2), 85.03 (s, diast. 1), 81.75 (s, diast. 2), 80.00 (d, diast. 1), 79.80 (d, diast. 2), 36.48 (s, diast. 1), 36.27 (s, diast. 2), 28.96 (q), 28.59 (q), 28.18 (q), 27.71 (q), 27.64 (q), 27.24 (q), 24.29 (q), 21.17 (q).

EIMS: m/z (%) = 217 (5, M^+), 130 (100).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.92; H, 9.31.

5-Benzyl-2,2,4-trimethyl-1,3-dioxolane-4-carboxylic Acid (7):
According to General Procedure 2, 2,3-dihydroxy-2-methyl-4-phenylbutanoic acid was obtained from **5** (2.80 g, 11.2 mmol). Yield 1.69 g, 72%, one diastereoisomer. White solid, mp. 150–155 °C. One part of the acid (1.00 g, 0.47 mmol) was converted into **7** (0.71 g, 60%, one diastereoisomer). Pale yellow solid, mp. 120–125 °C.

IR (KBr): ν = 2991 (s, br), 1707 (s) cm^{-1}.

^{1}H NMR: δ = 10.75–9.25 (s (br), OH), 7.43–7.15 (m, 5 arom. H), 4.19 (dd, J = 9.6, 3.1 Hz, $PhCH_2CH$), 3.07 (dd, J = 14.7, 3.1 Hz, PhC*H*H), 2.84 (dd, J = 14.7, 9.6 Hz, PhCH*H*), 1.64 (s, Me), 1.56 (s, Me), 1.40 (s, Me).

^{13}C NMR: δ = 176.47 (s), 137.89 (s), 128.99 (d), 128.39 (d), 126.56 (d), 110.19 (s), 84.90 (d), 83.30 (s), 36.15 (t), 26.93 (q), 25.99 (q), 22.62 (q).

EIMS: m/z (%) = 251 (100, [M + 1]+), 175 (36).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.09; H, 7.15.

5-(*tert*-Butyl)-2,2,4-trimethyl-1,3-dioxolane-4-carboxylic Acid (8):
According to General Procedure 2, 2,3-dihydroxy-2,4,4-trimethylpentanoic acid (48 mg, 55%, mixture of diastereoisomers) was obtained from **6** (108 mg, 0.50 mmol). White solid, mp. 122–123.5 °C. The acid (466 mg, 2.65 mmol) was then converted into **8** (410 mg, 72%, mixture of diastereoisomers).

IR (KBr): ν = 2990 (s, br), 2690 (m, br), 1713 (s), 1378 (s), 1226 (s) cm^{-1}.

^{1}H NMR: δ = 3.84 (s, *t*-BuC*H*, diast. 1), 3.71 (s, *t*-BuC*H*, diast. 2), 1.60 (s, *Me*CCOOH, diast. 2), 1.59 (s, *Me*CCOOH, diast. 1), 1.49 (s, Me), 1.49 (s, Me), 1.06 (s, *t*-Bu, diast. 1), 1.05 (s, *t*-Bu, diast. 2).

^{13}C NMR: δ = 176.85 (s, diast. 1), 176.63 (s, diast. 2), 108.20 (s, diast. 2), 107.95 (s, diast. 1), 92.84 (d, diast. 1), 87.02 (d, diast. 2), 83.33 (s, diast. 2), 82.28 (s, diast. 1), 33.11 (s, diast. 2), 32.42 (s, diast. 1), 28.02 (q), 27.11 (q), 26.85 (q), 26.05 (q), 25.49 (q), 25.40 (q), 20.45 (q).

EIMS: m/z (%) = 217 (26, [M + 1]+), 171 (33), 159 (84), 41 (53), 117 (22), 103 (21), 71 (100), 59 (76), 41 (99).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.02; H, 9.26.

2-(5-Benzyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)-1-(2-pyridylsulfanyl)ethyl Phenyl Sulfone (9):
According to General Procedure 3, from **7** (395 mg, 1.83 mmol). FC (Et_2O/hexane 1:1) of the crude product gave a yellow oil containing phenyl vinyl sulfone (167 mg) and **9** (283 mg, 32%, mixture of four diastereoisomers).

^{1}H NMR (characteristics peaks): δ = 6.05–5.85 (m, PySC*H*), 4.25–3.98 (m, $PhCH_2CH$), 3.50–2.55 + 2.40–1.75 (m, $PhCH_2$ + $PhSO_2CHCH_2$), 1.49 (s, Me), 1.40 (s, Me), 1.34 (s, Me), 1.26 (s, Me), 1.22 (s, Me), 1.13 (s, Me).

2-[5-(tert-Butyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl]-1-(2-pyridylsulfanyl)ethyl Phenyl Sulfone (10):
According to General Procedure 3, from **8** (123 mg, 0.57 mmol). FC (Et_2O/hexane 1:1) of the crude product gave **10** (90 mg, 35%, mixture of four diastereoisomers). White solid, mp 109–113 °C.

IR (KBr): ν = 2986 (m, br), 1313 (m), 1148 (s) cm^{-1}.

^{1}H NMR: δ = 8.30–8.13 (m, 1 arom. H), 7.89–7.84 (m, 2 arom. H), 7.50–7.22 (m, 4 arom. H), 7.12–6.68 (m, 2 arom. H), 6.05–5.83 (m, $PhSO_2CH$), 3.64 and 3.42 (2s, *t*-BuC*H*), 2.74 (dd, J = 15.8, 1.7 Hz, $PhSO_2CH_2CH_2$), 2.54 (d, J = 15.4 Hz, $PhSO_2CH_2CH_2$); 2.25–2.05 (m, $PhSO_2CH_2CH_2$), 1.33 (s, Me), 1.23 (s, Me), 1.02 (s, Me), 0.95 (s, Me).

EIMS: m/z (%) = 450 (6, M^+), 250 (19), 171 (33), 138 (24), 112 (43), 78 (27), 57 (49), 43 (100).

Anal. Calcd for $C_{23}H_{31}O_4S_2N$: C, 61.44; H, 6.95; N, 3.12. Found: C, 61.29; H, 7.13; N, 3.17.

l- and u-2-(5-Benzyl-2,2,4-trimethyl-1,3-dioxolan-4-yl)ethyl Phenyl Sulfone (11):
According to General Procedure 4, from **9** (240 mg, 0.50 mmol) containing phenyl vinyl sulfone (360 mg). FC (Et_2O/hexane 1:2) of the crude product gave **11** (173 mg, 95%, *l*-**11**/*u*-**11** 71:29 mixture of diastereoisomers). GC (SE 54, 230°C): *l*-**11**: retention time, 13.09 min; *u*-**11**: retention time, 13.38 min. Colorless liquid.

l-**11**:
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87–7.82 (m, 2 arom. H), 7.70–7.64 (m, 1 arom. H), 7.60–7.52 (m, 2 arom. H), 7.30–7.18 (m, 5 arom. H), 3.95 (dd, J = 8.3, 5.1 Hz, $PhCH_2CH$), 3.25–3.14 (m, $PhSO_2CH_2$), 2.96 (dd, J = 14.4, 8.3 Hz, $PhCHH$), 2.64 (dd, J = 14.3, 5.1 Hz, $PhCHH$), 1.79–1.66 (m, $PhSO_2CH_2CH_2$), 1.41 (s, Me), 1.23 (s, Me), 1.15 (s, Me).
^{13}C NMR: δ = 138.94 (s), 137.55 (s), 133.65 (d), 129.27 (d), 128.87 (d), 128.53 (d), 128.07 (d), 127.98 (d), 126.64 (d), 107.36 (s), 82.49 (d), 80.54 (s), 51.84 (t), 35.53 (t), 31.45 (t), 28.49 (q), 26.76 (q), 21.21 (q).

u-**11**:
^{1}H NMR (characteristic peaks): δ = 4.02 (dd, J = 8.4, 5.1 Hz, $PhCH_2CH$), 3.45–3.22 (m, $PhSO_2CH_2$), 2.20–2.00 (m, $PhSO_2CH_2CH_2$), 1.28 (s, Me), 1.21 (s, Me), 1.00 (s, Me).

Mixture of diastereoisomers:
IR (film): ν = 2984 (m, br), 1305 (s), 1221 (s, br) 1150 (s), 1086 (s) cm^{-1}.
^{13}C NMR: δ = 139.01 (s, *l*-diast.), 137.56 (s, *l*-diast.), 133.66 (d), 133.59 (d, *u*-diast.), 129.22 (d, *l*-diast.), 128.49 (d, *l*-diast.), 127.95 (d, *l*-diast.), 126.60 (d, *l*-diast.), 126.53 (d, *l*-diast.), 107.35 (s, *l*-diast.), 84.41 (d), 82.49 (d, *u*-diast.), 80.52 (s, *l*-diast.), 51.84 (t, *u*-diast.), 51.67 (t), 35.55 (t, *l*-diast.), 31.51 (t, *l*-diast.), 28.48 (q, *l*-diast.), 26.73 (q, *u*-diast.), 26.62 (q), 22.56 (q), 21.20 (q, *u*-diast.).
CI-MS: m/z (%) = 375 (8, M^+), 318 (20), 317 (100), 299 (15), 225 (7), 213 (11), 175 (26), 157 (24), 41 (47).
Anal. Calcd for $C_{21}H_{26}O_4S$: C, 67.35; H, 7.00. Found: C, 67.46; H, 6.96.

l- and u-2-[5-(*tert*-Butyl)-2,2,4-trimethyl-1,3-dioxolan-4-yl]ethyl Phenyl Sulfone (12):
According to General Procedure 4, from **10** (225 mg, 0.50 mmol). FC (Et_2O/hexane 1:1) of the crude product gave **12** (112 mg, 66%, *u*-**12**/*l*-**12** 86:14 mixture of diastereoisomers). GC (SE 54, 230°C): *l*-**12**: retention time, 4.05 min; *u*-**12**: retention time, 4.23 min. White solid, mp 109–111°C.

u-**12**:
^{1}H NMR: δ = 7.98–7.87 (m, 2 arom. H), 7.72–7.50 (m, 3 arom. H), 3.32 (s, *t*-BuCH), 3.30–3.20 (m, $PhSO_2CH_2$), 2.13–1.81 (m, $PhSO_2CH_2CH_2$), 1.35 (s, Me), 1.21 (s, Me), 1.13 (s, Me), 0.98 (s, *t*-Bu).
^{13}C NMR: δ = 139.35 (s), 133.63 (d), 129.27 (d), 128.00 (d), 105.35 (d), 88.50 (d), 80.90 (s), 52.22 (t), 32.80 (s or t), 32.42 (s or t), 28.35 (q), 27.36 (q), 26.45 (q), 22.69 (q).

Mixture of diastereoisomers:
IR (KBr): ν = 2986 (br s), 1383 (m), 1318 (s), 1289 (s), 1148 (s), 1084 (s) cm^{-1}.
^{13}C NMR: δ = 139.23 (s, *u*-diast.), 133.62 (d, *u*-diast.), 129.22 (d, *u*-diast.), 129.09 (d), 127.95 (d, *l*-diast.), 105.31 (s, *u*-diast.), 90.65 (d, *l*-diast.), 88.39 (d, *l*-diast.), 80.83 (s, *u*-diast.), 52.17 (t, *l*-diast.), 51.96 (t), 32.72 (s or t, *u*-diast.), 32.37 (s or t, *u*-diast.), 32.15 (s or t, *l*-diast.), 28.33 (q, *u*-diast.), 27.46 (q, *l*-diast.), 27.31 (q, *u*-diast.), 26.41 (q, *u*-diast.), 23.89 (q, *l*-diast.), 22.65 (q, *u*-diast.).
CIMS: m/z (%) = 341 (44, $[M+1]^+$), 283 (47), 213 (100).
Anal. Calcd for $C_{18}H_{28}O_4S$: C, 63.50; H, 8.29. Found: C, 63.58; H, 8.26.

Methyl 2-Methyl-4-phenylbut-2-enoate (13):[21]
Phenylacetaldehyde (0.94 mL, 4.20 mmol) was added at r.t. to a solution of methyl 2-(triphenylphosphoranylidene)propionate (0.70 g, 2.01 mmol) (prepared by aq NaOH treatment of the crude phosphonium salt in CH_2Cl_2) in CH_2Cl_2 (3.0 mL). The yellow solution was left at r.t. overnight and the solvent was then evaporated. FC (Et_2O/hexane 1:10) of the crude product afforded **13** (320 mg, 86%, one isomer) as a yellow liquid.
IR (film): ν = 1714 cm^{-1}.
^{1}H NMR: δ = 7.38–7.13 (m, 5 arom. H), 6.93 (tq, J = 7.6, 1.5 Hz, C=CH), 3.74 (s, MeO), 3.53 (d, J = 7.6 Hz, $PhCH_2$), 1.97 (d, J = 1.5 Hz, Me).
^{13}C NMR: δ = 168.43 (s), 140.29 (d), 138.92 (s), 128.61 (d), 128.43 (d), 128.17 (s), 126.34 (d), 51.66 (q), 34.81 (t), 12.47 (q).
EIMS: m/z (%) = 190 (37, M^+), 131 (100).
Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.83; H, 7.41.

3-Benzyl-2-methyl-2-oxiranecarboxylic Acid (14):
A dried ($MgSO_4$) solution of MCPBA (371 mg, 1.18 mmol) in CH_2Cl_2 (10 mL) was added to **13** (225 mg, 1.18 mmol). The solution was heated under reflux for 24 h and then allowed to cool down to r.t. KF (280 mg, 4.82 mmol) was added and the resulting mixture stirred overnight, filtered through Celite and the solvent evaporated. FC (Et_2O/hexane 1:6) of the crude product afforded methyl 3-benzyl-2-methyl-2-oxiranecarboxylate (161 mg, 66%, one diastereoisomer) as a colorless liquid.
IR (film): ν = 1738 (s) cm^{-1}.
^{1}H NMR: δ = 7.41–7.18 (m, 4 arom. H), 3.74 (s, MeO), 3.52–3.38 (X of ABX, $PhCH_2CH$), 2.99 (dd, A of ABX, J = 14.9, 6.2 Hz, $PhCHH$), 2.88 (dd, B of ABX, J = 14.9, 6.3 Hz, $PhCHH$), 1.67 (s, Me).
^{13}C NMR: δ = 171.54 (s), 136.53 (s), 128.67 (d), 126.77 (d), 62.24 (d), 57.66 (s), 52.47 (q), 34.42 (t), 13.67 (q).
EIMS: m/z (%) = 206 (18, M^+), 137 (71), 91 (89), 43 (100).
Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.68; H, 6.84.

A solution of $LiOH \cdot H_2O$ (66 mg, 1.56 mmol) in H_2O (1.3 mL) was added at 0°C to a solution of methyl 3-benzyl-2-methyl-2-oxiranecarboxylate (161 mg, 0.78 mmol) in THF (6.0 mL). The solution was left at 0°C for 6 h. The solvent was evaporated, the residue diluted with H_2O (20 mL) and washed with CH_2Cl_2 (3 × 10 mL). The aqueous layer was cooled down to 0°C, acidified with cold 5% aq HCl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to give **14** (140 mg, 93%, one diastereoisomer). Colorless liquid. The product was unstable and not suitable for elemental analysis.
^{1}H NMR: δ = 7.45–7.18 (m, 5 arom. H), 6.09 (t, J = 6.1 Hz, $PhCH_2CH$), 2.96 (d, J = 6.1 Hz, $PhCHH$), 2.94 (d, J = 6.0 Hz, $PhCHH$), 1.68 (s, Me).
EIMS: m/z (%) = 192 (16, M^+), 147 (82), 91 (100).

3-(*tert*-Butyl)-2-methyl-2-oxiranecarboxylic Acid (15):[22]
A cooled (−78°C) solution of 2-chloropropionic acid (2.71 g, 25.0 mmol) in THF (138 mL) was added to 1 M LDA (50.0 mmol) generated in situ by addition of BuLi (1.6 M/hexane, 31 mL, 50.0 mmol) to diisopropylamine (7.1 mL, 50.0 mmol) in THF (12 mL). After 5 min, pivalaldehyde (2.15 g, 25.0 mmol) in THF (15 mL) was added at −78°C. The cooling bath was then removed and the resulting mixture was allowed to warm to r.t.. The reaction was quenched by adding H_2O (31 mL). The organic layer was separated and washed with H_2O (2 × 30 mL) and brine. The combined aqueous layers were cooled in a dry ice/EtOH bath and acidified to pH 2 with cold 25% aq H_2SO_4. The cold bath was removed and CH_2Cl_2 (25 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (1 × 25 mL, 3 × 10 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$), filtered and evaporated to give **15** (2.89 g, 73%, 1.9:1.0 mixture of diastereoisomers) which was used without further purification in the next step. For analytical purpose, **15** was recrystallized in CH_2Cl_2. White solid, mp 82–84°C.

IR (film): ν = 2964, 1737, 1484, 1367, 1099, 1026, 867 cm^{-1}.

^1H NMR: δ = 10.40–9.80 (s (br), OH), 2.90 (s, *t*-BuC*H*, maj.), 2.79 (s, *t*-BuC*H*, min.), 1.69 (s, Me, maj.), 1.58 (s, Me, min.), 1.07 (s, *t*-Bu, maj.), 1.00 (s, *t*-Bu, min.).

^{13}C NMR: δ = 177.02 (s, maj.), 175.19 (s, min.), 73.39 (d, min.), 69.87 (d, maj.), 60.18 (s, min.), 58.2 (s, min.), 3.90 (s, maj.), 31.61 (s, min.), 27.43 (q, maj.), 26.08 (q, min.), 21.17 (q, min.), 13.60 (q, maj.).

CI-MS: *m/z* (%) –159 (11, M^+), 141 (20), 113 (9), 89 (14), 71 (100), 70 (14), 57 (11), 43 (75), 41 (32).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.75; H, 9.02.

2-(3-Benzyl-2-methyl-2-oxiranyl)-1-(2-pyridylsulfanyl)ethyl Phenyl Sulfone (16):
According to General Procedure 3, from **14** (96 mg, 0.50 mmol). FC (Et_2O/hexane 1:1) of the crude product gave **16** (112 mg, 53%, mixture of two diastereoisomers) as a yellow liquid.

IR (film): ν = 1578 (s), 1453 (s), 1418 (s), 1308 (s), 1148 (s) cm^{-1}.

^1H NMR : δ = 8.29–8.15 (m, 1 arom. H), 7.83–7.78 (m, 2 arom. H), 7.50–7.10 (m, 4 arom. H), 5.92 (dd, J = 5.8, 3.3 Hz, $PhSO_2CH$, diast. 1), 5.86 (t, J = 3.6 Hz, $PhSO_2CH$, diast. 2), 3.13–2.57 (m, 4 H, $PhCH_2CH + PhSO_2CHCHH$), 2.20–2.10 (m, $PhSO_2CHCHH$, diast. 1 or 2), 1.78–1.58 (m, $PhSO_2CHCHH$, diast. 1 or 2), 1.49 (s, Me, diast. 1), 1.47 (s, Me, diast. 2).

^{13}C NMR: δ = 154.20 (s, diast. 2), 154.03 (s, diast. 1), 149.02 (t), 137.64 (s), 137.24 (s), 136.58 (s), 136.25 (t), 133.60 (t, diast. 1), 133.2 (t, diast. 2), 129.77 (t), 128.83 (t), 128.68 (t), 128.53 (t), 128.26 (t), 128.17 (t), 126.47 (t, diast. 1), 126.36 (t, diast. 2), 122.42 (t, diast. 1), 122.29 (t, diast. 2), 120.53 (t), 65.02 (d), 62.55 (d), 62.23 (d), 61.92 (d), 59.07 (s), 36.39 (t), 35.82 (t), 35.22 (t), 34.85 (t), 17.06 (q, diast. 1), 16.73 (q, diast. 2).

CI-MS: *m/z* (%) = 426 (58, [M + 1]+), 284 (48), 189 (36), 143 (57), 112 (94), 96 (100), 91 (31), 41 (27).

Anal. Calcd for $C_{23}H_{23}S_2O_3N$: C, 64.92; H, 5.45. Found: C, 65.00; H, 5.52.

2-[3-(*tert*-Butyl)-2-methyl-2-oxiranyl]-1-(2-pyridylsulfanyl)ethyl Phenyl Sulfone (17):
According to General Procedure 3, from **15** (79 mg, 0.50 mmol). FC (Et_2O/hexane 1:2) of the crude product gave **17** (77 mg, 33%, mixture of two diastereoisomers) containing phenyl vinyl sulfone (344 mg) as a yellow liquid.

^1H NMR (characteristic peaks): δ = 5.99–5.82 (m, $PhSO_2CH$), 2.90 (dd, J = 13.8, 2.8 Hz, $PhSO_2CHCH_2$, diast. 2), 2.70 (dd, J = 14.7, 3.5 Hz, $PhSO_2CHCHH$, diast. 1), 2.59 (s, *t*-BuC*H*, diast. 2), 2.55 (s, *t*-BuC*H*, diast. 1), 2.04 (dd, J = 14.8, 11.1 Hz, $PhSO_2CHCHH$, diast. 1), 1.50 (s, Me, diast. 1), 1.45 (s, Me, diast. 2), 0.97 (s, *t*-Bu, diast. 1), 0.87 (s, *t*-Bu, diast. 2).

***l*-2-(3-Benzyl)-2-methyl-2-oxiranyl)ethyl Phenyl Sulfone (*l*-18)**:
According to General Procedure 4, from **16** (80 mg, 0.19 mmol). FC (Et_2O/hexane 1:1) of the crude product gave ***l*-18** (50 mg, 83%) as a colorless liquid.

IR (film): ν = 1449 (m), 1308 (s), 1152 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.95–7.88 (m, 2 arom. H), 7.73–7.58 (m, 3 arom. H), 7.38–7.18 (m, 5 arom. H), 3.21–3.14 (m, $PhSO_2CH_2$), 2.96 (t, J = 6.2 Hz, $PhCH_2CH$), 2.91 (dd, J = 14.6, 6.2 Hz, PhC*H*H), 2.84 (dd, J = 14.6, 6.1 Hz, PhCH*H*), 2.21–2.14 (m, $PhSO_2CH_2CHH$), 2.00–1.90 (m, $PhSO_2CH_2CHH$), 1.41 (s, Me).

^{13}C NMR: δ = 138.97 (s), 137.32 (s), 133.82 (d), 129.34 (d), 128.71 (d), 128.63 (d), 128.00 (d), 126.72 (d), 63.42 (d), 62.38 (s), 51.88 (t), 34.91 (t), 30.85 (t), 17.00 (q).

***l*-2-[3-(*tert*-Butyl)-2-methyl-2-oxiranyl]ethyl Phenyl Sulfone (*l*-19)**:
According to General Procedure 4, from **17** (85 mg, 0.22 mmol) containing phenyl vinyl sulfone (415 mg). FC (Et_2O/hexane 1:1) of the crude product gave ***l*-19** (45 mg, 74%) as a colorless liquid.

IR (film): ν = 1308 (s), 1150 (s) cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.95–7.80 (m, 2 arom. H), 7.70–7.63 (m, 1 arom. H), 7.62–7.53 (m, 2 arom. H), 3.34–3.12 (m, $PhSO_2CH_2$), 2.42 (s, *t*-BuC*H*), 1.92–1.85 (m, $PhSO_2CH_2CH_2$), 1.37 (s, Me), 0.99 (s, *t*-Bu).

^{13}C NMR: δ = 138.80 (s), 133.82 (d), 129.35 (d), 128.03 (d), 71.51 (d), 59.60 (s), 52.23 (t), 33.06 (t), 31.41 (s), 24.59 (q), 17.35 (q).

CI-MS: *m/z* (%) = 283 (47, $[M + 1]^+$), 227 (100).

HRMS (EI, $C_{15}H_{22}O_3S$, MH^+): calcd 283.1368, found 283.1357.

***u*-3-(tert-Butyl)-2-methyl-2-oxiranyl 2-Pyridyl Sulfide (*u*-20)**:
Tributylphosphine (0.43 mL, 1.49 mmol) was added under N_2 at 0°C to a solution of **15** (180 mg, 1.14 mmol) and 2,2′-dithiopyridine-1,1′-dioxide (376 mg, 1.49 mmol) in CH_2Cl_2 (4.0 mL). The solution was left 1 h at 10°C in the dark, diluted with CH_2Cl_2 (19 mL) and irradiated with a sun lamp (300 W) for 2 h at 10°C. The organic layer was washed with aq $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated. FC (Et_2O/hexane 1:8) of the crude product afforded ***u*-20** (91 mg, 36%). Pale yellow liquid.

IR (film): ν = 2963, 2360. 1712, 1579, 1557, 1454, 1415, 1365, 1150, 1121 cm^{-1}.

^1H NMR: δ = 8.38 (dm, J = 5.0 Hz, NC*H*), 7.47 (ddd, J = 8.1, 7.3, 1.9 Hz, NCH–CHC*H*), 7.20 (dt, J = 8.1, 1.0 Hz, NCH–CHCH–C*H*), 6.98 (ddd, J = 7.3, 5.0, 1.1 Hz, NCH–C*H*), 4.69 (s, *t*-BuC*H*), 2.34 (s, Me), 1.15 (s, *t*-Bu).

^{13}C NMR: δ = 157.86 (s), 149.08 (d), 13.98 (d), 122.22 (d), 122.17 (s), 119.71 (d), 61.44 (d), 34.14 (s), 30.98 (q), 28.10 (q).

EIMS: *m/z* (%) = 223 (29, M^+), 208 (54), 206 (47), 180 (85), 124 (86), 112 (100), 78 (49), 57 (27), 43 (88).

Anal. Calcd for $C_{12}H_{17}OSN$: C, 64.54; H, 7.67. Found: C, 64.23; H, 7.99.

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