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A New Synthesis of α-Asymmetric Nitroxide Radicals

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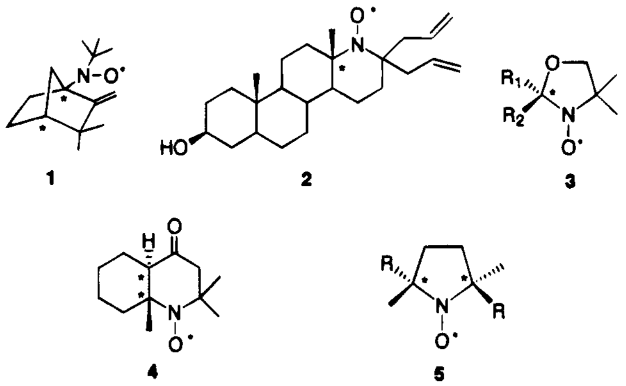
A new methodology for the synthesis of α-asymmetric bicyclic nitroxides is described. Reduction of certain homoallylic nitroenone with 3.0 equiv of SmI_2 in THF or THF−Et_2O at −50 °C gave a stable nitroxide radical−enolate intermediate, a kind of radical-anion species. The subsequent addition of electrophiles such as acyl chlorides at −50 °C resulted in the O-acylation of the enolate moiety to form the corresponding neutral nitroxide radical. The reduction process was quite sensitive to the substrate structure, amount of SmI_2, solvent composition, and reaction temperature. The optimum reaction conditions for this two-step reaction were determined. Analytically pure stable nitroxide radicals were isolated in good to fair yields when benzoyl chlorides substituted by electron-withdrawing groups were used as the electrophile for O-acylation. Although the use of organosilyl chlorides and alkylating reagents as the electrophile seemed to provide the corresponding radical products in the reaction mixture, pure radical products were not obtained. The mechanism of formation of the nitroxide radical−enolate intermediate was investigated by EPR spectroscopy and the product analysis.

Introduction

Among persistent or stable free radicals such as nitroxides,[1] verdazyls,[2] thioaminyls,[3] and certain hydrazyl[4] and phenoxyls,[5] nitroxide radicals show outstanding stability ascribed mainly to the lack of occurrence of dimerization.[6] For this reason sterically protected nitroxide radicals have been conventionally used as the stable free radical for spin-labeling and trapping experiments[7] and as the precursor of organic oxidants.[8] In addition, they have been regarded as a potential component for elaboration of purely organic, paramagnetic advanced materials due to the robust nature of the free radical.[9] In this context, it can be further expected that chiral nitroxide radicals bearing the quarternary asymmetric carbon center adjacent to the NO radical moiety would exhibit unique optoelectronic properties by the appropriate molecular design owing to the large dipole moment (μ = 3D) of the NO radical moiety, the magnetic moment arising from the unpaired electron and the molecular chirality. Irrespective of this consideration, there were a few synthetic methods for α-asymmetric nitroxide radicals (Chart 1). Optically active campheny1 and steroidal nitroxides **1** and **2** were derived from the corresponding optically active camphor and steroid.[10,11] Racemic DOXY's **3** were prepared from the β-amino alcohols and ketones.[12] Optically active decahydroquinoline nitroxides **4** were obtained from diastereomeric derivatives after optical resolution.[13] Pyrrolidine nitrox-

Chart 1



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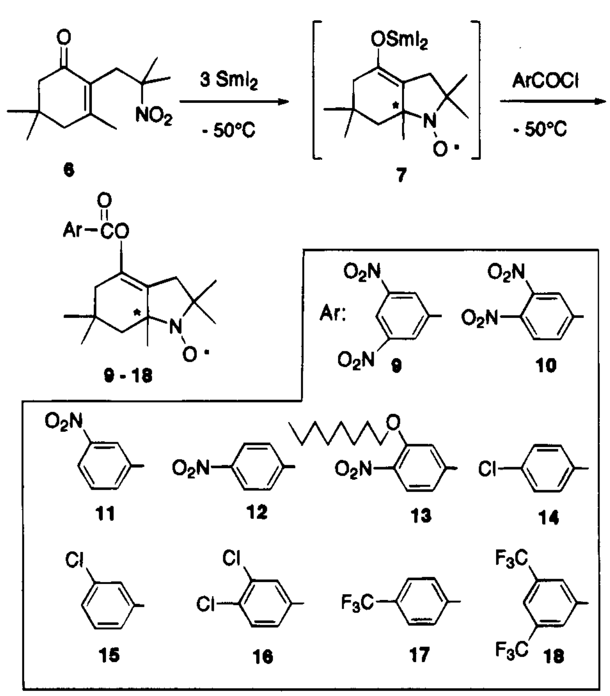
Scheme 1



ides 5 were obtained by the reaction of the corresponding nitrones with organometallic carbon nucleophiles.[14] These synthetic methods involve oxidation of the corresponding amine or hydroxylamine as the key step for generation of a nitroxide radical.

In this connection, quite recently we have found a new, direct synthetic method of α-asymmetric bicyclic nitroxide radicals by reduction of homoallylic nitroenone **6** followed by the reaction with nitro-substituted benzoyl chlorides (Scheme 1). We have reported the unique crystal properties of the obtained nitroxides, in which spontaneous optical resolution quite rare with respect to free radicals was observed.[15] With the aim of elaboration of paramagnetic chiral organic advanced materials such as liquid crystals containing a chiral nitroxide radical moiety as a paramagnetic center in the core portion,[16] we have surveyed the scope and limitations of this synthetic method for α-asymmetric nitroxide radicals. In this account we describe these results and discuss the reaction mechanism.

Results and Discussion

During investigation of the mechanism of a newly found S$_{RN}$1 reaction affording homoallylic nitroenone **6**,[17] we observed the formation of α-asymmetric nitroxide **9** by reduction of homoallylic nitroenone **6** followed by the reaction with 3,5-dinitrobenzoyl chloride **8** (Scheme 1). Since this is considered to be a two-step reaction involving radical-enolate intermediate **7**, we searched the optimum reaction conditions for both processes of the reduction of **6** and subsequent substitution by the enolate moiety of **7**. Then the best reaction conditions were applied to other substrates and electrophiles.

Table 1. Optimization of Reaction Conditions (Scheme 1)

entry	SmI$_2$ (equiv)	solvent (Et$_2$O vs THF, v/v)	temp (°C)	**9**, yield (%)[a]
1	2.0	1:2	−78	0
2	2.5	1:2	−78	10
3	3.0	1:2	−78	37
4	3.0	1:3	−78	40
5	4.0	1:3	−78	5
6	3.0	1:5	−78	18
7	3.0	THF	−78	<5
8	3.0	1:3	−50	75
9	3.0	1:3	0	32

[a] Determined by HPLC analysis.

Optimum Reaction Conditions. Among the reducing agents examined, SmI$_2$ having moderate reducing ability ($E^{ox}_{1/2}$ −1.55 V vs SCE)[18] toward **6** ($E^{red}_{1/2}$ −1.68 V) was the best choice. Powerful reducing agents such as Li and Na naphthalenides led to poor results, due to their too strong reducing ability ($E^{ox}_{1/2}$ −2.5V)[19] resulting in overreduction of **7**. As summarized in Table 1, this reaction was quite sensitive to the amount of SmI$_2$, solvent composition, reaction temperature, and the manner of addition of **8**. The strict use of 3 equiv or a little bit more of SmI$_2$ (until the blue color of SmI$_2$ developed) was essential for completion of the reaction. The use of THF alone as the solvent led to poor results. Reaction at lower or higher temperatures than −50 °C both in reduction and addition of **8** led to decreased yields of **9**. Addition of a solution of **8** in THF or Et$_2$O produced only a trace amount of **9**. Thus, the best yield (75%) of **9** was achieved when **6** was treated with 3 equiv of SmI$_2$ in the mixed solvent of THF and Et$_2$O (3:1, v/v) at −50 °C followed by the addition of powdered **8** all at once at −50 °C and warming to 25 °C. Necessity of such delicate reaction conditions can be interpreted in terms of mechanism of the formation and reaction of radical-enolate intermediate **7**. The consumption of 3 equiv of SmI$_2$ is in accord with the formation of **7** by three-electron reduction of **6**. Competition between the electron transfer reaction from **7** to **8** and the desirable addition−elimination reaction (O-acylation) of **7** with **8** seems to be responsible for the observed solvent effects, since the reduction potential of **8** ($E^{red}_{1/2}$ > −0.81 V)[19] must be higher than the oxidation potential of radical-enolate **7**. Thus, the use of Et$_2$O and the heterogeneous reaction conditions for the O-acylation could effectively serve to suppress the undesired electron transfer reaction, instead giving rise to O-acylation product **9** predominantly.

Preparation of α-Asymmetric Bicyclic Nitroxides. By virture of the above optimum reaction conditions, several α-asymmetric nitroxides were prepared by using nitro-substituted benzoyl chlorides in good yield as shown in Table 2 (Scheme 1). For isolation of the products, the

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Table 2. Preparation of α-Asymmetric Nitroxide Radicals (Scheme 1)

entry	ArCOCl	product	mp (°C)	% yield	EPR data g	EPR data a_N (gauss)
1	$3,5\text{-}(NO_2)_2C_6H_3COCl$ (**8**)	**9**	147.5−148.5	75	2.0058	14.6
2	$3,4\text{-}(NO_2)_2C_6H_3COCl$	**10**	125.9−127.3	65	2.0058	13.9
3	$3\text{-}NO_2C_6H_4COCl$	**11**	65.1−65.9	65	2.0058	14.8
4	$4\text{-}NO_2C_6H_4COCl$	**12**	138.4−139.9	45	2.0058	13.9
5	$3\text{-}C_8H_{17}O\text{-}4\text{-}NO_2\text{-}C_6H_3COCl$	**13**	a	60	2.0060	14.7
6	$4\text{-}ClC_6H_4COCl$	**14**	a	80	2.0060	14.6
7	$3\text{-}ClC_6H_4COCl$	**15**	36.0−37.2	45	2.0060	14.6
8	$3,4\text{-}Cl_2C_6H_3COCl$	**16**	a	50	2.0059	14.7
9	$4\text{-}CF_3C_6H_4COCl$	**17**	74.2−75.1	50	2.0060	14.7
10	$3,5\text{-}(CF_3)_2C_6H_3COCl$	**18**	a	60	2.0060	14.9

[a] Obtained as an oily material.

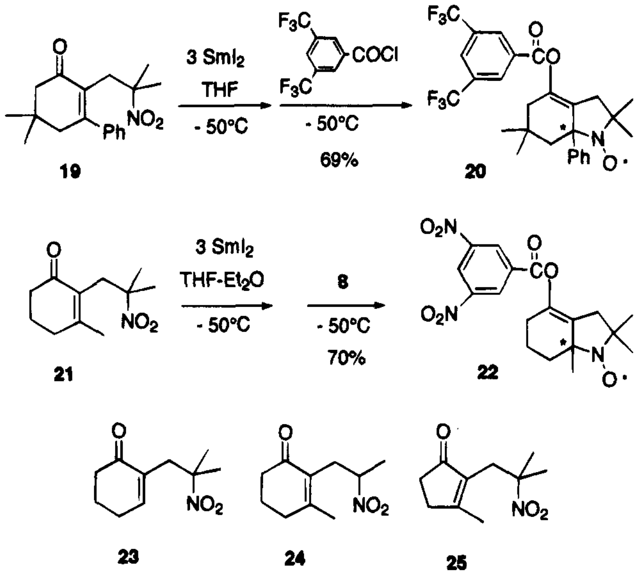
resulting reaction mixture was filtered to remove the insoluble materials, and the filtrate was concentrated and subjected to flash column chromatography. The molecular structures of nitroxides **9**, **11**, and **12** were unequivocally established by X-ray crystallographic analysis.[15] Their EPR spectral data measured in THF are also summarized in Table 2. The radical purity of solid materials **9**, **11**, and **12** was determined to be approximately >95% by magnetic susceptibility measurements.[15] As a preliminary experiment for elaboration of purely organic paramagnetic liquid crystals, introduction of 4-nitro-3-(octyloxy)benzoyl moiety by O-acylation was accomplished, giving nitroxide **13** (entry 5).

Benzoyl chlorides substituted by other electron-withdrawing groups such as the chlorine and trifluoromethyl groups were also the appropriate electrophile for O-acylation of **7**. In these cases, either of the use of THF alone as the solvent and the addition of a THF solution of the benzoyl chloride derivative did not affect the yield of nitroxides, because the undesired electron transfer reaction is no longer a predominant reaction pathway. The nitroxide radicals obtained are summarized in Table 2 along with thier EPR spectral data measured in THF.

Although O-silylation of **7** by organosilyl chlorides such as dimethylphenylsilyl chloride and dimethyl-*tert*-butylsilyl chloride seemed to provide the corresponding radical products in the reaction mixture as was confirmed by EPR spectroscopy, pure radical products were not obtained by the above nonaqueous workup procedure probably due to their instability. Likewise, acetyl chloride, trifluoroacetic anhydride, triethyloxonium tetrafluoroborate, and ethyl triflate failed to give pure O-acylation or alkylation products, despite the probable formation of the radical products.

As to the structure of homoallylic nitroenones that can undergo the successive reduction and O-acylation, there are three mandatory requirements. First, the presence of an alkyl (aryl) substituent on β-carbon atom of the enone moiety is necessary. Secondly, the carbon atom bearing a nitro group must be quarternary. These two requirements are essential for the formation of stable di-*tert*-alkyl nitroxides. Thirdly, the substrate must assume a geometry which allows short intramolecular contact between the nitro group and the ethylenic β-carbon atom of the enone moiety[20] so as to effect rapid intramolecular cyclization as shown in the following section. Nitroenones **19** and **21** satisfying these requirements led to the formation of analogous stable α-asymmetric nitroxides (Scheme 2), whereas compounds **23**−**25** lacking any of the above conditions failed to give the desired nitroxides. It is noteworthy that phenyl-substituted nitroenone **19** participates in the substrates for the successful radical formation reaction, because compatibility of an aryl group at this position is useful in view of elaboration of purely organic paramagnetic liquid crystals.

Scheme 2



Mechanism. There are two possible reaction pathways for formation of radical-enolate **7** which are consistent with the experimental results described above (pathways a and b in Scheme 3). In pathway a, homoallylic nitroenone **6** undergoes one-electron reduction by SmI_2. The electron should be incorporated into π^*-orbital of the NO_2 group, the LUMO, to generate the radical-enolate of **6**. The resulting nucleophilic nitro oxygen anion effects intramolecular 1,4-addition to the proximate enone moiety to give **26**,[17] followed by additional two-electron reduction and rearrangement to form stable radical-enolate **7** through oxyaminyl radical **28** and allyl radical **29**.[21] Alternatively, in pathway b, initial three-electron reduction of the nitro group produces the nitroso radical anion **27**. Either of subsequent intramolecular 1,4-addition of oxygen anion of **27** to the enone moiety followed by rearrangement via the intermediacy of **28** and **29** or direct intramolecular 1,4-addition of nitrogen radical or anion of **27** to the enone moiety gives the same

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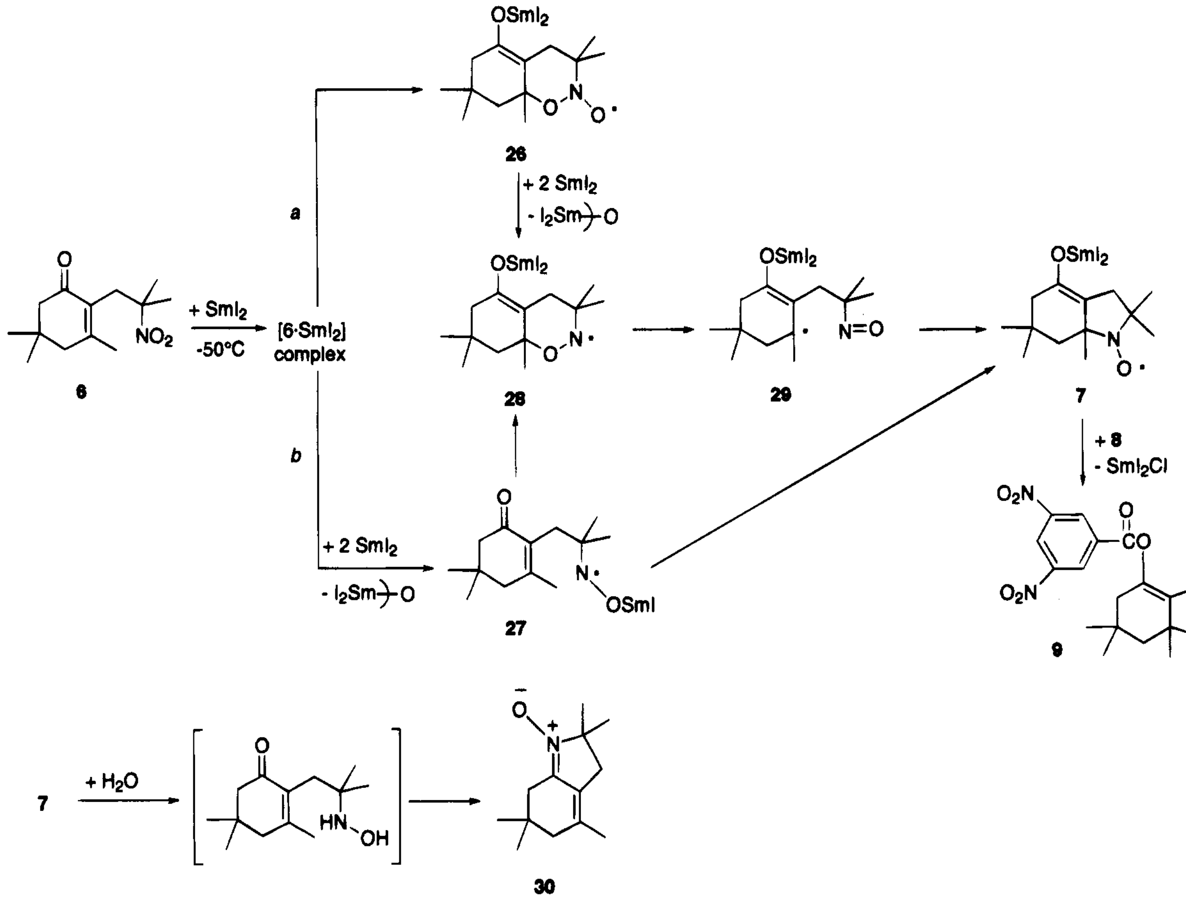
Scheme 3



radical-enolate **7**. In order to examine which is a more plausible pathway (a or b), the process of formation of **7** was followed by EPR spectroscopy by changing the reaction temperature and the amount of added SmI_2 and at the same time the product analysis was performed. When 1 equiv of SmI_2 was added to a THF solution of **6** at −50 °C, only a very weak spectrum (a 1:1:1 triplet) corresponding to **7** (g = 2.006, a_N = 14.4 gauss) was observed. After aqueous workup of this reaction mixture at −50 °C, **6** was obtained in more than 99% recovery. As the reaction temperature was slowly raised, the spectral intensity gradually increased until drastic increase was noted at around −10 °C. By aqueous workup at −10 °C or higher, a 1:3 mixture of **30** and **6** was obtained (Scheme 3). Since reduction of **6** with 3.0 equiv of SmI_2 in MeOH−THF at 25 °C produced the same product **30** in 75% yield,[22] **30** is definitely formed by intramolecular cyclization of the corresponding amino alcohol followed by dehydration. In contrast, addition of 3.0 equiv of SmI_2 to a THF solution of **6** at −50 °C led to detection of the fairly intense EPR spectrum of **7**. Aqueous workup of this reaction at −50 °C provided a 3:1 mixture of **30** and **6** together with a small amount of unidentified reduction products. These results indicate that at −50 °C only complexation between **6** and 1 equiv of SmI_2 occurred and disproportionation of the **6**−SmI_2 complex occurred promptly above −10 °C, while addition of 3 equiv of SmI_2 led to the formation of **7** even at −50 °C. Furthermore, although the use of 3 equiv or a little bit more of SmI_2 (until the blue color of SmI_2 developed) resulted in the best product yield as shown in Table 1 (entry 8), it is clear that overreduction of **7** still occurred to some extent even in the reaction with 3 equiv of SmI_2 at −50 °C. Since no other EPR spectrum than that of **7** was observed under any condition, it is conclusive that either process to give **26** or **27** must be the rate-determining step and the forming reaction of **7** from **26** or **27** was too rapid to detect any other radical intermediate by EPR spectroscopy. It has been shown that di-*tert*-butyl oxyaminyl radical is a persistent radical species.[21] However, oxyaminyl radical **28** would be fairly unstable and rearrange rapidly due to its allylic structure, even if it is formed as an intermediate. Thus, it is still unclear which intermediate **26** or **27** is the actual one.

Conclusions

We have described a new synthetic method for α-asymmetric bicyclic nitroxide radicals that are expected to act as a paramagnetic center in elaboration of paramagnetic chiral organic advanced materials. Synthesis of paramagnetic organic liquid crystals by using this methodology is under investigation, together with application of this synthetic method to asymmetric synthesis of chiral nitroxides.

Experimental Section

Infrared spectra were recorded as liquid films on NaCl plates or as KBr pellets. ^1H NMR spectra were recorded at 400 MHz, and ^{13}C NMR were recorded at 100 MHz; $CDCl_3$ was used as the solvent. EPR spectra were recorded at −50 to 25 °C; the magnetic field sweep of the spectrometer was calibrated using a solution of Fremy's salt in saturated aqueous $NaHCO_3$ [a_N: 13.091 G, g: 2.0055]. HPLC analysis was carried out by using a silica gel stationary-phase column (YMC-Pack SIL-06, 0.46 × 30 cm) and UV-vis spectrometer

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(254 nm) as the detector. All solvents were distilled before use. All reactions were run under Ar.

Homoallylic nitroenones **21**, **23**, **24** and **25** were prepared according to a published procedure.[23]

Preparation of 6. A mixture of isophorone (124 g, 0.90 mol), thiophenol (99.2 g, 0.90 mol), aqueous 35% formaldehyde (125 mL, 1.58 mol), and triethanolamine (134 g, 0.90 mol) was heated at reflux for 4 days. After cooling to 25 °C, the reaction mixture was extracted with ether (3 × 70 mL). The combined organic phase was washed successively with aqueous 5% NaOH solution (3 × 100 mL), brine (3 × 100 mL), and H_2O (100 mL), dried over $MgSO_4$, and concentrated in vacuo to give 216 g (92%) of a brown oil, crude 3,5,5-trimethyl-2-[(phenylthio)methyl]-2-cyclohexen-1-one: IR (neat) 1665, 1585, 1482, 1440 cm^{-1}; ^1H NMR δ 7.63−7.20 (m, 5H), 3.96 (s, 2H), 2.30 (s, 4H), 1.88 (s, 3H), 1.00 (s, 6H).

To this crude oil (23.1 g, 88.8 mmol) dissolved in MeOH (355 mL) was added dropwise an aqueous solution of oxone (81.9 g, 0.266 mol, in 100 mL of H_2O) at 0 °C. The reaction mixture was vigorously stirred at 25 °C for 1 h and diluted with H_2O (200 mL). The aqueous mixture was extracted with CH_2Cl_2 (6 × 100 mL). The combined organic phase was washed with H_2O (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was recrystallized from the mixed solvent of CH_2Cl_2 (50 mL) and hexane (50 mL) to give 17.8 g (76%) of the white crystals, 3,5,5-trimethyl-2-[(phenylsulfonyl)methyl]-2-cyclohexen-1-one: IR (KBr) 1665, 1450, 1325, 1305, 1140 cm^{-1}; ^1H NMR δ 7.90−7.49 (m, 5H), 4.42 (s, 2H), 2.13 (s, 4H), 1.73 (s, 3H), 0.95 (s, 6H).

A mixture of this crystalline material (17.5 g, 60 mmol) and $LiCMe_2NO_2$ (8.55 g, 90 mmol) in DMF (180 mL) was irradiated with visible light (400-W tungsten lamp; through a Pyrex-brand flask) at 25 °C for 70 h under argon atmosphere with vigorous stirring. To this reaction mixture was added aqueous saturated NH_4Cl solution (200 mL), and the aqueous mixture was extracted with ether (3 × 100 mL). The combined organic phase was washed with brine (3 × 100 mL) and H_2O (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by recrystallization from EtOH to give 12.9 g of **6** (90%) as the white crystals.

6: mp 51.2−52.3 °C; IR (KBr) 1660, 1620, 1537, 1365 cm^{-1}; ^1H NMR δ 3.01 (s, 2H), 2.26 (s, 4H), 1.84 (s, 3H), 1.53 (s, 6H), 1.04 (s, 6H); ^{13}C NMR δ 198.4, 158.2, 129.0, 88.3, 50.9, 47.2, 35.4, 32.1, 28.1, 20.0, 21.8. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H,8.84; N, 5.85. Found: C, 65.51; H,8.63; N, 6.07.

Preparation of 19. A mixture of dimedone (13.0 g, 92.7 mmol), paraformaldehyde (3.07 g, 106 mmol), and $PhSO_2Na{\cdot}2H_2O$ (18.6 g, 92.7 mmol) in glacial acetic acid (93 mL) was heated at reflux for 22 h. After cooling to 25 °C, H_2O (200 mL)was added, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with brine (3 × 50 mL) and H_2O (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was recrystallized from ether to give 22.3 g (82%) of the red crystals, 5,5-dimethyl-3-hydroxy-2-[(phenylsulfonyl)methyl]-2-cyclohexen-1-one: IR (KBr) 2600, 1718, 1634, 1306, 1139 cm^{-1}; ^1H NMR δ 8.85 (br, 1H), 7.70−7.20 (m, 5H), 4.20 (s, 2H), 2.10 (s, 4H), 1.05 (s, 6H).

To this crystalline material (22.3 g, 75.6 mmol) in CH_2Cl_2 (90 mL) was added Et_3N (9.18 g, 90.7 mmol) at 0 °C. After stirring at 0 °C for 15 min, methoxymethyl chloride (12.2 g, 151 mmol) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. The organic mixture was diluted with additional CH_2Cl_2 (100 mL), washed with H_2O (60 mL), dried over $MgSO_4$, and concentrated in vacuo to give 24.5 g (100%) of a white solid, crude 5,5-dimethyl-3-[(methoxymethyl)oxy]-2-[(phenylsulfonyl)methyl]-2-cyclohexen-1-one: IR (KBr) 1730, 1630, 1310, 1150 cm^{-1}; ^1H NMR δ 8.00−7.25 (m, 5H), 5.05 (s, 2H), 4.15 (s, 2H), 3.30 (s, 3H), 2.46 (s, 2H), 2.04 (s, 2H), 1.05 (s, 6H).

A mixture of this solid material (25.0 g, 77.2 mmol) and $LiCMe_2NO_2$ (11.0 g, 116 mmol) in DMF (150 mL) was stirred under irradiation with visible light (400-W tungsten lamp; through a Pyrex-brand flask) at 25 °C for 3 days under argon atmosphere. To this reaction mixture was added aqueous saturated NH_4Cl solution (200 mL), and the aqueous mixture was extracted with ether (3 × 100 mL). The combined organic phase was washed with brine (3 × 100 mL) and H_2O (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was purified by recrystallization from EtOH to give 11.3 g (51%) of the white crystals, 5,5-dimethyl-3-[(methoxymethyl)oxy]-2-(2-methyl-2-nitropropyl)-2-cyclohexen-1-one: IR (KBr) 1722, 1540, 1370 cm^{-1}; ^1H NMR δ 5.00 (s, 2H), 3.55 (s, 3H), 3.10 (s, 2H), 2.60 (s, 2H), 2.30 (s, 2H), 1.60 (s, 6H), 1.25 (s, 6H).

To this crystalline material (3.00 g, 10.5 mmol) in MeOH (25 mL) was added a drop of concd H_2SO_4. After stirring at 25 °C for 1 min, the solvent was removed in vacuo. The residue was dissolved in $CHCl_3$ (50 mL), dried over $MgSO_4$, and the solvent was concentrated in vacuo to give 2.54 g (100%) of a white solid, crude 5,5-dimethyl-3-hydroxy-2-(2-methyl-2-nitropropyl)-2-cyclohexen-1-one; IR (KBr) 2675, 1717, 1625, 1538, 1382 cm^{-1}; ^1H NMR δ 7.01 (br, 1H), 2.92 (s, 2H), 2.31 (s, 4H), 1.46 (s, 6H), 1.05 (s, 6H).

To this solid material (6.89 g, 28.6 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (3.47 g, 34.3 mmol) at 0 °C. After stirring at 0 °C for 10 min, $(CF_3SO_2)_2O$ (8.87 g, 31.4 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 30 min, and aqueous 50% $NaHCO_3$ solution (50 mL) was added. The aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phase was washed with H_2O (40 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting solid was recrystallized from ether/hexane to give 6.82 g (70%) of the white crystals, 5,5-dimethyl-2-(2-methyl-2-nitropropyl)-3-[(trifluoromethylsulfonyl)oxy]-2-cyclohexen-1-one: IR (KBr) 1697, 1663, 1539, 1427, 1375, 1317, 1138 cm^{-1}; ^1H NMR δ 3.03 (s, 2H), 2.61 (s, 2H), 2.33 (s, 2H), 1.51 (s, 6H), 1.25 (s, 6H).

To a solution of this crystalline material (0.342 g, 1.00 mmol) in THF (10 mL) was added dropwise a preformed solution of Ph_2CuLi (1.10 mmol) in THF via cannula at −78 °C. The reaction mixture was stirred at −78 °C for 3 h, and aqueous saturated NH_4Cl solution (50 mL) was added at this temperature. After warming to 25 °C, the aqueous mixture was extracted with ether (3 × 50 mL). The combined organic phase was washed with brine (30 mL) and H_2O (30mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give 0.110 g (35%) of **19** as pale yellow crystals.

19: mp 47.2−48.6 °C; IR (KBr) 1670, 1540, 1350 cm^{-1}; ^1H NMR δ 7.42−7.09 (m, 5H), 3.02 (s, 2H), 2.54 (s, 2H), 2.40 (s, 2H), 1.34 (s, 6H), 1.14 (s, 6H); ^{13}C NMR δ 199.1, 159.5, 140.4, 129.9, 128.5, 128.1, 126.9, 88.0, 50.9, 48.6, 35.2, 32.6, 28.1, 26.2. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H,7.69; N, 4.65. Found: C, 71.88; H,7.80; N, 4.42.

General Procedure for Preparation of α-Asymmetric Nitroxide Radicals (9−13 and 22) in THF/Et$_2$O. To a solution of the homoallylic nitroenone **6** or **21** (2.00 mmol) in the mixed solvent of ether (25 mL) and THF (15 mL) was dropwise added a freshly prepared THF solution of SmI_2 (ca. 0.10 M solution; 60 mL)[18] at −50 °C under argon atmosphere, followed by stirring for additional 10 min at the same temperature. The powdered nitro-substituted benzoyl chloride (3.00 mmol) was added all at once to the yellowish brown solution at −50 °C. The resulting red solution was slowly allowed to warm to room temperature over 1 h. After removal of the yellowish brown precipitate by filtration in the air, the filtrate was concentrated to give viscous oily red material, which was dissolved in $CHCl_3$ and subjected to short flash column chromatography on silica gel (19:1 hexane/ethyl acetate) to remove Sm-containing components. The crude organic product was purified by flash column chromatography on silica gel (19:1 hexane/EtOAc) judging the eluent by means of HPLC analysis to give the analytically pure nitroxide radical.

9: IR (KBr) 1729, 1544, 1455, 1362, 1346, 1158 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_3O_7$: C, 57.41; H, 5.78; N, 10.04. Found: C, 57.22; H, 5.97; N, 9.78.

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10: IR (KBr) 1744, 1545, 1460, 1374, 1350, 1185 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_3O_7$; C, 57.41; H, 5.78; N, 10.04. Found: C, 57.70; H, 5.92; N, 10.31.

11: IR (KBr) 1741, 1534, 1457, 1369, 1350, 1198 cm^{-1}. Anal. Calcd for $C_{20}H_{25}N_2O_5$; C, 64.33; H, 6.75; N, 7.50. Found: C, 64.05; H, 6.70; N, 7.79.

12: IR (KBr) 1739, 1530, 1460, 1363, 1349, 1190 cm^{-1}. Anal. Calcd for $C_{20}H_{25}N_2O_5$; C, 64.33; H, 6.75; N, 7.50. Found: C, 64.21; H, 6.78; N, 7.36.

13: IR (neat) 1742, 1531, 1424, 1375, 1360, 1200 cm^{-1}. Anal. Calcd for $C_{27}H_{38}N_2O_6$: C, 67.04; H, 8.24; N, 5.58. Found: C, 63.88; H, 8.19; N, 5.45.

22: IR (KBr) 1738, 1544, 1458, 1363, 1345, 1158 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_3O_6$: C, 55.38; H, 5.16; N, 10.76. Found: C, 55.64; H, 5.33; N, 10.93.

General Procedure for Preparation of α-Asymmetric Nitroxide Radicals (14 −18 and 20) in THF. To a solution of the homoallylic nitroenone **6** or **19** (2.00 mmol) in THF (40 mL) was added dropwise a freshly prepared THF solution of SmI_2 (60 mL, 6.0 mmol)[18] at −50 °C under argon atmosphere, followed by stirring for additional 10 min at the same temperature. A solution of the chloro- or trifluoromethyl-substituted benzoyl chloride (3.00 mmol) in THF (3 mL) was added to the yellowish brown solution at −50 °C. The resulting red soution was slowly allowed to warm to room temperature over 1 h. The isolation of the pure nitroxide radical was carried out in a similar manner to the above procedure.

14: IR (neat)1740, 1455, 1370, 1198, 1090 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3Cl$: C, 66.20; H, 6.94; N, 3.86. Found: C, 65.95; H, 7.12; N, 4.06.

15: IR (KBr) 1740, 1452, 1372, 1195, 1105 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3Cl$: C, 66.20; H, 6.94; N, 3.86. Found: C, 65.99; H, 6.66; N, 4.06.

16: IR (neat) 1740, 1468, 1382, 1200, 1108 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_3Cl$: C, 60.46; H, 6.09; N, 3.53. Found: C, 60.23; H, 6.04; N, 3.78.

17: IR (KBr) 1742, 1455, 1372, 1326, 1269, 1169, 1138, 1109 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_3Cl$: C, 63.63; H, 6.36; N, 3.53. Found: C, 63.35; H, 6.42; N, 3.28.

18: IR (neat) 1750, 1462, 1388, 1283, 1241, 1183, 1142 cm^{-1}. Anal. Calcd for $C_{22}H_{24}NO_3F_6$: C, 56.90; H, 5.21; N, 3.02. Found: C, 56.71; H, 4.91; N, 2.77.

20: IR (neat) 1736, 1460, 1361, 1280, 1257, 1182, 1140 cm^{-1}. Anal. Calcd for $C_{27}H_{26}NO_3F_6$: C, 61.60; H, 4.98; N, 2.66. Found: C, 60.32; H, 4.87; N, 2.47.

Preparation of 30. To a solution of **6** (0.240 g, 1.00 mmol) in the mixed solvent of THF (4 mL) and MeOH (2 mL) was dropwise added a freshly prepared THF solution of SmI_2 (30 mL, 3.0 mmol) at 25 °C under argon atmosphere. After stirring for 3 min at 25 °C, the reaction mixture was poured into aqueous 10% $Na_2S_2O_3$ solution (100 mL). The aqueous mixture was extracted with ethyl acetate (3 x 50 mL). The combined extract was dried over $MgSO_4$, and the solvent was concentrated in vacuo. The crude material (0.220 g), which was a ca. 3:1 mixture of **30** and **6**, was subjected to column chromatography on silica gel (EtOAc) to give 0.050 g (24%) of **30** as an amber oil. **30**: IR (neat) 1580, 1162 cm^{-1}; ^1H NMR δ 2.61 (s, 2H), 2.35 (s, 2H), 1.98 (s, 2H), 1.71 (s, 3H), 1.45 (s, 6H), 0.99 (s, 6H); ^{13}C NMR δ 143.3, 129.7, 124.6, 73.2, 45.6, 37.5, 34.6, 31.2, 28.6, 26.4, 19.4; mass specrum, *m/e* 207 (p). Anal. Calcd for $C_{13}H_{25}NO_3$ as the dihydrate: C, 64.17; H, 10.35; N,5.76. Found: C, 64.94; H,9.32; N,5.96.

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