3.6 (1 H, A part of an ABX, CH_2N).

Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 65.01; H, 7.44; N, 7.21.

1-(*N*-Isopropylamino)-3-(1-naphthyloxy)-2-propanol (17a). Propranolol is usually isolated as its hydrochloride (see refs 18 and 19). White solid: mp 91-92 °C (recryst. Et_2O). IR (CCl_4), cm-1: ν_{OH} and ν_{NH} = 3620, 3440. ^1H NMR ($CDCl_3$), δ ppm: regioisomer **17a** (100%), 8.25 (1 H, m, H arom); 7.80 (1 H, m, H arom); 7.40 (4 H, m, H arom); 6.85 (1 H, dd, H arom); 4.15 (3 H, m, A^1B^1C part of an A^1B^1CXY, OCH_2CH-); 3.00 (1 H, X part of an A^1B^1CXY, J_{XY} = 12 Hz, $J_{CX} \approx 3$ Hz, CH_2N); 2.75 (1 H, sept CH); 2.70 (1 H, Y part of an A^1B^1CXY, J_{XY} = 12 Hz, $J_{CY} \approx 6.5$ Hz, CH_2N); 1.1 (6 H, d, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$), δ ppm: 154.3 (C arom); 134.4 (C arom); 127.4, 126.3, 125.7, 125.1, 121.7, 120.5 104.8 (7 CH arom); 70.7 (CH_2O); 68.4 (CHO); 49.5 (CH_2N); 48.8 (CHN); 23 (2 CH_3).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.09; H, 8.16; N, 5.39. Found: C, 74.28; H, 8.03; N, 5.25.

2-[3',4'-(Methylenedioxy)phenyl]oxirane (13). To a solution of trimethylsulfonium iodide (8 g, 40 mmol) in anhydrous THF (30 mL) was added NaH (0.95 g, 40 mmol), and the mixture was heated to 60 °C for 2 h. Then a solution of piperonal (4.5 g, 30 mmol) in THF (30 mL) was added dropwise. At the end of the addition, the mixture (pink) was stirred at 60 °C until no piperonal remained as shown by TLC (about 2 h). After addition of H_2O (15 mL) THF was evaporated under vacuum and the remaining aqueous phase was extracted with pentane (5 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give the epoxide (85%) which was used without further purification. The physical characteristics of 2-[3',4'-(methylenedioxy)phenyl]oxirane (13) corresponded to the known values.[17]

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Nitrones from Addition of Benzyl and Allyl Grignard Reagents to Alkyl Nitro Compounds: Chemo-, Regio-, and Stereoselectivity of the Reaction

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Reaction of allyl and benzyl Grignard reagents with functionalized nitroalkanes affords nitrones in good yield. This process shows considerable chemoselectivity; carbonyl groups and other highly reactive electrophilic functions are unaffected by the reaction conditions (THF, -70 °C). A mixture of regioisomers **4** and **5** is usually obtained, and the product distribution depends on the nature of the alkyl framework. An intermediate **3** is postulated, and the isomeric pair of nitrones arises, very likely through a selective syn elimination. α-Substituted alkyl chains give mostly conjugated products **4** while unbranched chains afford predominantly the nonconjugated nitrones **5**. The **4**/**5** ratio can be strongly modified by using a proton source of suitable strength; trichloroacetic acid produces **4** exclusively in the reaction of nitroethane with benzyl Grignard, while 2,6-dimethylphenol affords completely the nonconjugated nitrone **5**. The stereochemistry of the double bond is affected by the nature of the reagent used. Benzyl Grignard gives only *Z* nitrones **4** and **5**; 2-butenylmagnesium chloride gives nonconjugated *Z* nitrones and a predominance of *E* isomer in the conjugated nitrone **5**.

Recent years have witnessed a significant increase in the utilization of nitrones as highly valuable synthetic intermediates[1] and as useful spin trapping reagents.[2] In particular, nitrones can be considered versatile 1,3 dipoles for the construction of nitrogen heterocycles which constitute the backbone of various biologically active compounds.[3]

Addition of Grignard and lithium reagents to nitrones, although less explored, represents an alternative application of these compounds in synthesis.[4] This reaction was recently applied to the synthesis of enantiomerically pure amino and hydroxylamino derivatives, since it proceeds with high diastereoselectivity when an appropriate stereogenic group is placed close to the nitrogen atom of the parent nitrone.[5]

Several synthetic methods for nitrones have been reported, but very few of them show general applicability. Classical methods involve the condensation of N-monosubstituted hydroxylamines with carbonyl compounds[6] or direct oxidation of N,N-disubstituted hydroxylamines.[7]

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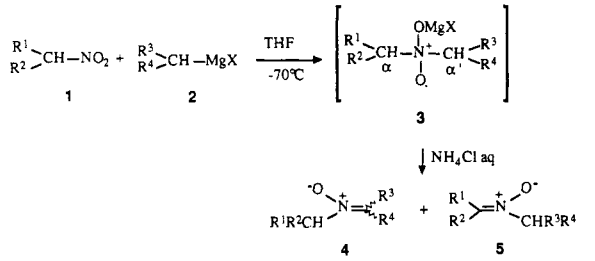
Table I. Reaction of Grignard Reagents and Nitro Compounds in THF at −70 °C and then Quenching with NH_4Cl_{aq}

entry	nitro compd	Grignard reagent	product		overall yield (%)	4:5 ratio (%)	Z:E[a] ratio (%)
1	1b	2b	4bb		58		
2	1c	2b	4cb	5cb	68	85:15	
3	1d	2a	4da	5da	65	7:93	15:85
4	1d	2b	4db	5db	75	39:61	
5	1e	2a	4ea	5ea	72	10:90	21:79
6	1e	2b		5eb	74		
7	1f	2a	4fa		78		12:88
8	1f	2b	4fb		74		
9	1g	2b	4gb	5gb	70	39:61	
10	1h	2a	4ha	5ha	61	35:65	30:70
11	1i	2b	4ib	5ib	75	40:60	
12	1j	2a	4ja		70		15:85
13	1j	2b	4jb		71		
14	1k	2a	4ka		69		25:75
15	1k	2b	4kb		66		
16	1l	2a		5la	71		
17	1l	2b		5lb	75		
18	1m	2a	4ma	5ma	81	20:80	15:85

[a] Referred to product 4. Benzyl Grignard gives only Z nitrones, and 2-butenylmagnesium chloride gives only nonconjugated (Z)-5 nitrones.

Scheme I

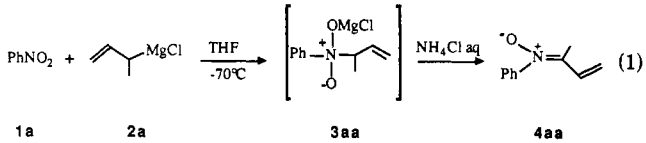


1b; $R^1=R^2=H$ 1h; R^1=2-FurylCH_2, $R^2=H$ 2a; $R^3=CH_2=CH$, $R^4=CH_3$
1c; $R^1=CH_3$, $R^2=H$ 1i; $R^1=CH_3CH(Cl)CH_2$, $R^2=H$ 2b; $R^3=Ph$, $R^4=H$
1d; R^1=n-C_3H_7, $R^2=H$ 1j; $R^1=CH_3COCH_2CH_2$, $R^2=CH_3$
1e; R^1=n-C_5H_{11}, $R^2=H$ 1k; $R^1=CH_3O_2CCH_2CH_2$, $R^2=CH_3$
1f; $R^1=R^2=CH_3$ 1l; $R^1=(CH_3)_2CH$, $R^2=H$
1g; $R^1=CH_3COCH_2$, $R^2=H$ 1m; $R^1=C_6H_5$, $R^2=H$

Unfortunately, the preparation of functionalized hydroxylamines has been found to be a problematic process. The recently reported oxidation of readily available secondary amines seems to be a more reliable procedure.[8] However oxidation methods[9] cannot be applied or require controlled conditions when other oxidizable functions are present in the substrate. N-alkylation of oximes is a somewhat attractive process but it is often foiled by a competitive O-alkylation.[10]

More recently, other systems have been set up to synthesize this class of compounds: Michael addition of oximes to activated alkenes,[11] reaction of alkyl triflates with aldoxime O-trimethylsilyl ethers[12] and reaction of α-chloronitroso compounds with Grignard reagents.[13] Clearly, efforts to develop additional procedures for the synthesis of nitrones are still desirable, especially for those unobtainable by existing methods.

Recently, we reported that the reaction between nitro compounds and 2-butenylmagnesium chloride can provide a good approach to the synthesis of allylic nitrones.[14] For example, nitrobenzene (**1a**), when treated with 1 equiv of γ-methallylmagnesium chloride (**2a**), undergoes 1,2-addition to form a tetrahedral intermediate **3aa** which is decomposed to α-ethenyl-α-methyl-*N*-phenylnitrone (**4aa**) (eq 1). In our preliminary paper we focused our attention



1a 2a 3aa 4aa

mainly on the reactivity of aromatic nitro compounds, and less attention has been paid to the behavior of the aliphatic derivatives. In the present work we report on the reactivity of a large variety of alkyl nitro compounds with γ-methallyl and benzyl Grignard reagents with particular emphasis on chemo-, regio-, and stereoselectivity involved in nitrone formation.

Results and Discussion

Treatment of an aliphatic nitro compound **1b–m** with an equimolecular amount of γ-methallyl- (**2a**) or benzylmagnesium chloride (**2b**) at low temperature (−70 °C) in THF, followed by a proton source quenching, gives conjugated **4bb–ma** and/or nonconjugated **5cb–ma** nitrones (Scheme I). The *E* and *Z* stereochemistry of the nitrone products was assigned in the same way that was described in a previous paper.[14] Various protic quenchings have been examined; a slight excess of acetic acid in cold CH_2Cl_2 followed by addition of water or an aqueous saturated solution of ammonium chloride gave generally the best results. More acidic proton sources such as diluted HCl caused extensive nitrone hydrolysis, while less acidic ones such as aqueous potassium acetate gave poor yields. The

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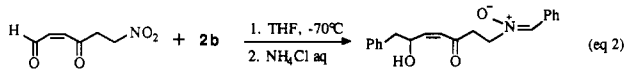
nature of the proton source can also affect the relative ratio of conjugated to nonconjugated nitrones. Due to the complexity of these results, they will be discussed later.

The results concerning nitrone formation under acetic acid or saturated solution of ammonium chloride quenching condition are summarized in Table I. They show that the reaction has general applicability and that in all cases examined good to high yields are obtained. It is worth noting that the reaction proceeds with high chemoselectivity. Groups highly reactive toward Grignard reagents such as chloro and carbonyl functions of ketones and esters are completely unaffected if the simple precaution, namely to slowly add magnesium reagent to the nitro compound, is used (entries 9, 11–15). An absolute selectivity is also observed even when the nitro group is sterically hindered by the presence of an alkyl group in the α-position, as in nitroketone **1j** (entries 12, 13).

The exclusive attack at the nitro function fails only in the reaction with compound **1n** where, under 1:1 substrate/RMgX molar ratio conditions, the compound **6nb** arising from double attack was isolated in 25% yield together with comparable amounts of unreacted material and products of mono attack both at the nitro and aldehydic function (eq 2). The use of a 2.5-equiv excess of RMgX



1n 6nb

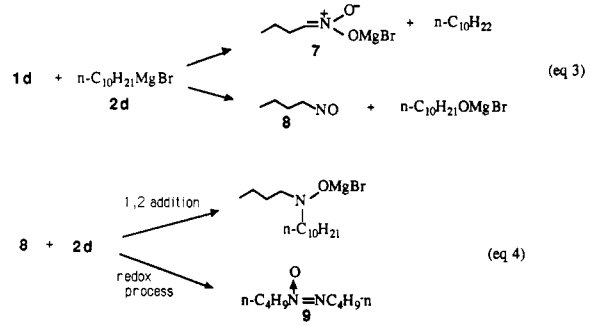
gave compound **6nb** in 81% yield. These results confirm that the nitro group is much more reactive with RMgX than carbonyl functions of esters and ketones, thus allowing a complete chemoselectivity control. On the other hand, nitro and aldehyde reactivity with RMgX are comparable.[15]

A literature survey suggests that nitrone formation is a reaction presumably restricted to allylic and benzylic reagents. It has been reported that in reactions of aliphatic nitro compounds with an excess of an alkylmagnesium halide (MeMgX, EtMgX, etc.) nitrone formation is negligible, the main process being reductive alkylation of the nitro group to form dialkylhydroxylamine.[16] A mechanism involving preliminary formation of a 1:1 adduct of type **3** followed by a slower Grignard-promoted reduction to the hydroxylamino derivative has been proposed.[17] This interpretation is in sharp contrast with recent results which show that allylmagnesium halides are unable to reduce intermediates of this type and that this process requires strong specific reducing agents such as $LiAlH_4$.[18]

It was recently found in the reaction of nitroarenes with phenyl[19] and vinyl[20] reagents that disubstituted hydroxylamine formation must very likely be ascribed to a 1,2-addition on the nitrosoarene intermediate formed by an initial attack of RMgX at the oxygen atoms of the parent nitro compound and subsequent fast elimination of ROMgX. Furthermore, we have observed that in several cases the nonconjugated nitrone, arising through proton removal from a saturated alkyl chain, is preferentially formed. It is therefore evident that an analogous pathway concerning saturated alkyl reagents would not reasonably involve an adduct of **3** as the main intermediate. Nevertheless, it is known that product distribution in reactions involving metallorganic reagents and strong electron acceptor substrates may change with experimental conditions;[21] hence, the reactivity of 1-nitrobutane (**1d**) with n-C_4H_9MgBr (**2c**), n-$C_{10}H_{21}MgBr$ (**2d**), and t-C_4H_9MgBr (**2e**) has been examined under the optimum conditions for our process.

In the reaction of **1d** we were able to observe formation of the following products: starting material (58%), axozybutane (28%) and trace amounts of azobutane, *n*-dibutylhydroxylamine, and α-propyl-*N*-butylnitrone. Formation of butane and butanol was also observed. However, an accurate yield determination of these two compounds was impossible due to the volatility of the former and to the solubility in water of the latter. Consequently, we examined the reaction of **1d** with a primary reagent bearing a heavier alkyl framework such as **2d**. The observed product distribution at a 1:1 substrate/RMgX molar ratio was substantially the same: **1d** (46%), axozybutane (26%), 1-decanol (46%), *n*-decane (32%), lesser amounts of azobutane, *N*-butyl-*N*-decylhydroxylamine, and 1-decene. The use of a 2-fold excess of RMgX with respect to **1d** caused an increase in azo and azoxy compound yields. However, a considerable amount of starting nitro compound was again recovered (25%). Further addition of RMgX caused mainly an increase in azo compound at the expense of azoxy derivative.

These findings suggest that two competitive processes can occur: the first one consists of the removal of the acidic proton in the α-position with respect to the nitro group by Grignard base to give nitronate salt **7**. Alternatively, oxygen transfer can occur to form 1-nitrosobutane (**8**), which is more reactive than the parent nitro compound and can quickly undergo 1,2-addition or a redox process (eqs 3, 4).[22] In this context the reactivity of *t*-BuMgBr



(**2e**) is very significant. This carbanionic species was found to prefer attack on nitrogen rather than on oxygen or the ring carbon in the reaction with dinitrobenzene.[23]

Actually, when **1d** was allowed to react with **2e**, α-propyl-*N*-*tert*-butylnitrone (**10**) was isolated in 15% yield. However, while no reduction or reductive N-alkylation products were detected in the reaction mixture, the re-

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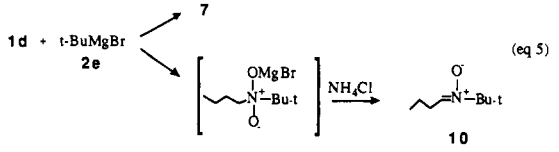
covery of a large amount of starting material (80%) even in the presence of a large excess of RMgX indicates that the prevailing process is the formation of magnesium nitronate salt **7** (eq 5). These results are not surprising



taking into account the high basicity and steric hindrance of this reagent. Unfortunately, the poor conversion of the starting nitro compound to the corresponding nitrone limits the synthetic utility of the reaction, since this class of nitrones is more available by other procedures. In conclusion, the attack on nitrogen seems to be the exclusive domain of carbanionic moieties possessing a π character. A similar pattern has been found in the aromatic series where the product distribution strongly depends on the nature of the carbanionic reagent.[21,24]

Several attempts to react allylmagnesium bromide with various nitro compounds led only to disappointing results since the crude material obtained from the reaction quickly polymerizes upon evaporation of the solvent, giving a sticky vitreous solid.[14] The formation of nitrone **13** has been confirmed in the reaction of 2-methylnitrobenzene with allylmagnesium bromide by exploiting a 1,3-dipolar cycloaddition process performed with acrylonitrile and the crude material in THF (Scheme II).

Stereo- and Regioselectivity. The reaction shows complex regiochemistry, leading generally to both possible regioisomers. In several cases the conjugated nitrone largely prevails and in others the nonconjugated does. Two hypotheses can be suggested: (i) There is a kinetic control in the elimination reaction promoted by acetic acid on intermediate **3**; i.e., the product distribution is governed by the relative facility of the conjugate base of the proton source to approach and to remove a proton in the α or in α' position. (ii) The relative amounts of **4** and **5** reflect their relative stability. The latter seems a less plausible interpretation since it may be expected that a conjugated nitrone is much more stable than the corresponding nonconjugated regioisomer. However, there are no extensive and exhaustive studies on this argument[1b] due to serious difficulty in analyzing experimentally the Behrend's equilibrium.[25]

In the case of phenyl nitrones like **4bb–kb** the repulsion in the *Z* configuration between the negative oxygen and the aromatic ring can constrain the phenyl group to assume an orthogonal conformation with consequent decrease in conjugative efficiency.[26] In order to evaluate the relative stability between **4** and **5**, we carried out some isomerization experiments. This process requires strong base catalysis; for example, nonconjugated nitrone **5da** is converted into the isomer **4da** in ethanol at reflux in the presence of ethoxide ion (see Table II). Unfortunately, under these drastic conditions extensive decomposition occurs. Although this prevents an accurate determination of the relative isomer stability, it is possible to argue from the data of Table II that the conjugated nitrone is largely more stable than the nonconjugated one. In fact, pure **5da** gave after 1 h a 30% conversion into **4da** with a recovery of 68% of nondecomposed material, while no isomerization

Scheme II

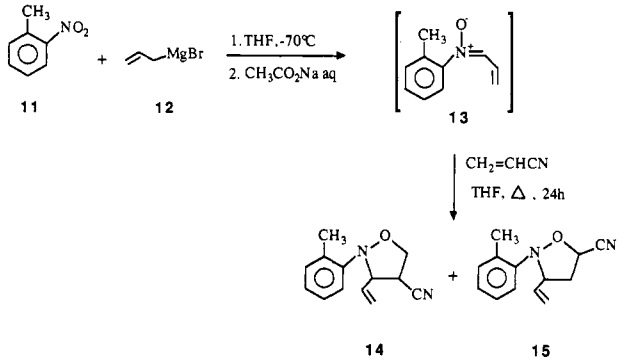


Table II. Isomerization of Nitrones in EtOH at Reflux in the Presence of EtONa

	time (min)	ratio 5da:4da	recovered 4da + 5da (%)
5da → 4da	0	100:0	100
	15	92:8	95
	30	83:17	87
	60[a]	70:30	68
4da → 5da	0	0:100	100
	15	0:100	80
	30[a]	0:100	52
	time (min)	ratio 4ma:5ma	recovered 4ma + 5ma (%)
4ma → 5ma	0	100:0	100
	10	83:17	85
	30[a]	60:40	73
5ma → 4ma	0	0:100	100
	10	4:96	80
	30[a]	10:90	70

[a] After this time extensive decomposition of the products occurs.

was detected at the same reaction time starting from pure **4da**. On the other hand, in the case of both conjugated isomers **4ma** and **5ma** an easy reciprocal interconversion was observed.

Despite the apparent complexity, the regio- and stereochemical outcome shows characteristic features. First, we will discuss the reaction with benzyl Grignard reagents. The relative amounts of regioisomers are strongly dependence on the structure of the alkyl substituent in the starting nitroalkane. The preference for the less stable isomer **5** increases with the length of the alkyl chain. Indeed, in the reaction of nitromethane (**1b**) with $PhCH_2MgCl$ (**2b**) the almost exclusive formation of conjugated isomer **4bb** was observed. On going from the ethyl to the *n*-hexyl nitro derivative, the yield of nonconjugated compound increased at the expense of the conjugated one, becoming in the last case the largely prevalent product (Table I). α-Alkyl substitution as in 2-nitropropane (**1f**) produced exclusively the conjugated isomer **4fb** (see also entries 13 and 15), while its β homologue **1l** gave, surprisingly, only the nonconjugated **5lb**.

Some speculation about a possible mechanism can be made assuming the formation of a tetrahedral nitrogen intermediate of type **3** in which magnesium is presumably coordinated with both oxygen atoms. The carbon–nitrogen bond length would be shorter than usual owing to the positive charge on the nitrogen and this, together with the low reaction temperature (−70 °C), would enhance the steric constraint on this intermediate. The positively charged nitrogen spreads its effects on the contiguous

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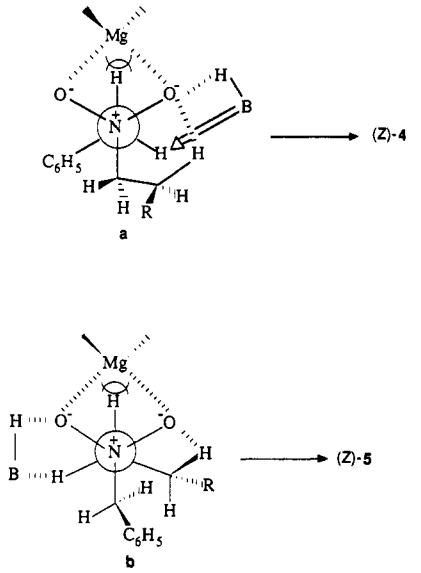

Figure 1. Proposed models for the selective proton abstraction in the reaction of nitroalkanes with benzyl Grignard reagent.

bonds, and so we feel that a hydrogen bonding between a hydrogen at the β carbon and one of the oxygen atoms could be very likely. This effect forces the larger groups (phenyl and alkyl chain) to be in the anti position.

It should be observed that the alkyl chain is able in all events to produce a certain degree of steric hindrance for the attack of the syn oxygen, allowing the formation of the conjugated product. It is known that elimination processes, in weakly ionizing solvents, involving good leaving groups, such as MgXOH, can proceed through a syn or anti mechanism, depending on the nature of the base–countercation ion pair.[27] The stereochemical outcome of this reaction strongly suggests a syn pathway, the only one by which a *Z* isomer could be formed (see Figure 1).

The ease of approach to the α and α' hydrogens by the proton donors determines the regiochemistry of the reaction. Benzylic hydrogens are more acidic and hindered than those in the alkyl group (Figure 1b), so we expect that a suitable modulation of the strength and bulkiness of the acid used could allow us to obtain selectively the two regioisomers. Results summarized in Table III for the reaction of nitroethane with benzylmagnesium chloride, at various conditions, show that trichloroacetic acid (entry 1) allows exclusive formation of the conjugated nitrone. Indeed, the parent base of this acid is rather weak, and so it acts selectively on the more acidic benzylic hydrogens. Different isomeric ratios are obtained with weaker acids, changing the steric crowding around the carboxylic group and confirming the expected trend. The possibility of a change in the mechanism of the reaction with an increase of E1 character, using different quenching conditions, must also be taken into account.

However, in the described conditions, we were unable to exert complete control over the regioisomeric distribution of products since the most favorable ratio concerning the nonconjugated isomer was 65/35 (Table III, entry 9). Therefore, we decided to employ substituted phenols since in our opinion there might be taken a double benefit from their use. Firstly, phenols form a stronger conjugate base, and secondly, groups placed in positions 2 and 6 in the aromatic ring are closer to the basic center, ensuring a sharper steric effect with respect to the α substituents of carboxylic acids. Experimental results confirm this assumption and show that the maximum effect is achieved with 2,6 dimethylphenol (entry 11) with which only the nonconjugated isomer is obtained.

Table III. Reaction of Benzylmagnesium Chloride (2b) and 1c in THF at −70 °C and then Quenching with Various Proton Sources

entry	proton source	overall[a] yield (%)	4cb:5cb ratio (%)
1	CCl_3CO_2H	50	100:0
2	$(CH_3)_3CCO_2H$	63	88:12
3	NH_4Cl_{aq}	71	85:15
4	Ts^-PyH^+	70	76:24
5	$2,4\text{-}Cl_2C_6H_3OH$	55	68:32
6	$2,4,6\text{-}Me_3C_6H_2CO_2H$	68	64:36
7	$(CH_3)_3CCH_2CO_2H$	68	61:39
8	Ph_2CHCO_2H	70	55:45
9	$2\text{-}Cl\text{-}3,5\text{-}(NO_2)_2C_6H_2CO_2H$	40	35:65
10	$2,4,6\text{-}Br_3C_6H_2OH$	50	35:65
11	$2,6\text{-}Me_2C_6H_3OH$	60	0:100

[a] Yields of pure isolated products.

It is highly probable that the reaction with 2-butenylmagnesium chloride follows the same pattern as with the benzyl Grignard reagent, although with some slight differences. As previously stated,[14] a simple alkyl chain gives mostly isomer of **5** of *Z* stereochemistry, but a more accurate analysis of the experimental results has established the existence of a small percentage of **4** (entries 3, 5, Table I). Also α substitution seems to have a critical effect in this case since only conjugated isomer **4** is formed, while the β analog (entry 16, Table I) shows a preference for **5**. The formation of **4** proceeds with lower selectivity compared to the benzyl reagent because there is only a small difference in energy between the two anti positions adopted by the alkyl chain with respect to the methyl and vinyl groups.

In conclusion, a detailed picture of the reaction of functionalized nitroalkanes with allylic and benzylic Grignard reagents has been made. This practical synthetic methodology for the preparation of nitrones shows good chemo-, regio-, and stereochemical features that can be enhanced with a proper choice of experimental conditions. The benzyl Grignard reagents usually display better selectivity over the 2-butenyl analog, although the latter has been successfully employed in the enantioselective synthesis of nitrones, starting from optically active nitroalkanes.[28] The present procedure is restricted to the use of allylic and benzylic reagents, and this represents the more obvious limitation of this synthetic methodology.

Experimental Section

^{1}H-NMR spectra were recorded at 300 MHz in $CDCl_3$. *J* values are given in Hz. Mass spectra were obtained using the EI technique. Reaction progress was monitored by TLC or capillary GLC. Melting points are uncorrected. Flash chromatography[29] was performed on Merck Silica gel (0.040–0.063 mm) eluting with hexane–ethyl acetate–ethanol (6:3:1).

All chemicals used are commercial, and literature methods were followed for the synthesis of 2-(β-nitroethyl)furan,[30] 3-chloro-1-nitrobutane,[31] and nitro ketones.[32] THF was dried by refluxing it over sodium wire until the blue color of benzophenone ketyl persisted and then distilling it into a dry receiver under nitrogen atmosphere.

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2-Butenylmagnesium chloride[33] and benzylmagnesium chloride[34] were prepared as described and titrated before use.[35]

Reaction between Nitro Compounds and Grignard Reagents. (*Z*)-α-Phenyl-*N*-methylnitrone (4bb). To a stirred THF solution (30 mL) of nitromethane (**1b**) (0.305 g, 5 mmol) at −70 °C was added benzylmagnesium chloride (**2b**) (5.5 mmol, 4.6 mL, 1.2 M in THF) under N_2. The mixture was stirred for 20 min and then was quenched with saturated aqueous NH_4Cl, extracted with ether, and dried ($MgSO_4$). Solvent was evaporated under reduced pressure, and the crude product was submitted to a flash-chromatographic purification (hexane–ethyl acetate–ethanol (6:3:1)) affording 0.392 g (58%) of nitrone **4bb** as a colorless oil: IR (cm^{-1}, neat) 1585 (C=N), 1160 (NO); ^1H NMR δ 3.85 (3 H, s), 7.35–7.42 (3 H, m, ArH + 1 H), 8.20–8.25 (2 H, m, ArH); MS *m/e* 135 (M^+), 134, 118, 107, 89, 77, 65. Anal. Calcd for C_8H_9NO (135.16): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.10; H, 6.73; N, 10.35.

(*Z*)-α-Phenyl-*N*-ethylnitrone (4cb): yield 58%; oil; IR (cm^{-1}, neat) 1595 (C=N), 1185 (NO); ^1H NMR δ 1.55 (3 H, t, *J* = 7.20), 3.96 (2 H, q, *J* = 7.20), 7.38–7.42 (3 H, m, ArH + 1 H), 8.20–8.25 (2 H, m, ArH); MS *m/e* 149 (M^+), 148, 131, 120, 105, 89, 77, 65. Anal. Calcd for $C_9H_{11}NO$ (149.19): C, 72.45; H, 7.43; N, 9.38. Found: C, 72.43; H, 7.40; N, 9.40.

(*Z*)-α-Methyl-*N*-benzylnitrone (5cb): yield 10%; oil; IR (cm^{-1}, neat) 1590 (C=N), 1175 (NO). ^1H NMR δ 2.47 (3 H, d, *J* = 4.64), 4.89 (2 H, s), 6.72 (1 H, q, *J* = 4.64), 7.38–7.43 (5 H, m, ArH); MS *m/e* 149 (M^+), 131, 119, 91, 77, 65, 41. Anal. Calcd for $C_9H_{11}NO$ (149.19); C, 72.45; H, 7.43; N, 9.38. Found: C, 72.48; H, 7.40; N, 9.40.

α-Ethenyl-α-methyl-*N*-butylnitrone (4da): yield 5%. *E* isomer: oil; IR (cm^{-1}, neat) 1585 (C=N), 1160 (NO); ^1H NMR δ 0.85 (3 H, t, *J* = 7.35), 1.45–1.65 (4 H, m), 2.20 (3 H, s), 4.05 (2 H, t, *J* = 7.30), 5.35–5.50 (2 H, m, CH_2=), 6.65–6.75 (1 H, m, –CH=); MS *m/e* 141 (M^+), 140, 124, 82, 68, 55, 41. Anal. Calcd for $C_8H_{15}NO$ (141.21): C, 68.04; H, 10.70; N, 9.91. Found: C, 68.05; H, 10.73; N, 9.91. *Z* isomer: oil; IR (cm^{-1}, neat) 1585 (N=O), 1165 (NO); ^1H NMR δ 0.85 (3 H, t, *J* = 7.35), 1.40–1.65 (4 H, m), 2.13 (3 H, s), 3.90 (2 H, t, *J* = 7.30), 5.55–5.70 (2 H, m, CH_2=), 7.32–7.45 (1 H, m, –CH=); MS *m/e* 141 (M^+), 140, 126, 124, 82, 68, 55, 41. Anal. Calcd for $C_8H_{15}NO$ (141.21): C, 68.04; H, 10.70; N, 9.91. Found: C, 68.05; H, 10.70; N, 9.93.

(*Z*)-α-Propyl-*N*-(1-buten-3-yl)nitrone (5da): yield 60%; oil; IR (cm^{-1}, neat) 1595 (C=N), 1165 (NO); ^1H NMR δ 0.95 (3 H, t, *J* = 7.35), 1.55 (3 H, d, *J* = 6.71), 2.40–2.50 (4 H, m), 4.40 (1 H, quint, *J* = 6.78), 5.25–5.30 (2 H, m, CH_2=), 6.00–6.15 (1 H, m, –CH=), 6.62 (1 H, t, *J* = 4.65); MS *m/e* 141 (M^+), 124, 113, 82, 68, 55, 41. Anal. Calcd for $C_8H_{15}NO$ (141.21): C, 68.04; H, 10.70; N, 9.91. Found: C, 68.02; H, 10.68; N, 9.88.

(*Z*)-α-Phenyl-*N*-butylnitrone (4db): yield 29%; mp 73 °C (from hexane); IR (cm^{-1}, KBr) 1595 (C=N), 1175 (NO); ^1H NMR δ 0.94 (3 H, t, *J* = 7.35), 1.50–1.55 (2 H, m), 2.40–2.50 (2 H, m), 3.75 (2 H, t, *J* = 7.40), 7.40–7.45 (3 H, m, ArH + 1 H), 8.27–8.32 (2 H, m, ArH); MS *m/e* 177 (M^+), 176, 160, 118, 104, 77, 65. Anal. Calcd for $C_{11}H_{15}NO$ (177.24): C, 74.54; H, 8.53; N, 7.90. Found: C, 74.53; H, 8.50; N, 7.93.

(*Z*)-α-Propyl-*N*-benzylnitrone (5db): yield 46%; oil; IR (cm^{-1}, neat) 1600 (C=N) 1160 (NO); ^1H NMR δ 0.95 (3 H, t, *J* = 7.30), 1.52–1.60 (2 H, m), 2.42–2.51 (2 H, m), 4.89 (2 H, s), 6.69 (1 H, t, *J* = 5.60), 7.38–7.43 (5 H, m, ArH); MS *m/e* 177 (M^+), 160, 149, 133, 91, 77, 65, 51. Anal. Calcd for $C_{11}H_{15}NO$ (177.24): C, 74.54; H, 8.53; N, 7.90. Found: C, 74.53; H, 8.50; N, 7.89.

(*Z*)-α-Pentyl-*N*-benzylnitrone (5eb): yield 74%; mp 79 °C (from hexane); IR (cm^{-1}, KBr) 1595 (C=N), 1170 (NO); ^1H NMR δ 0.88 (3 H, t, *J* = 7.40), 1.25–1.35 (4 H, m), 1.40–1.55 (2 H, m), 2.45–2.55 (2 H, m), 4.80 (2 H, s), 6.58 (1 H, t, *J* = 5.90), 7.40–7.45 (5 H, m, ArH); MS *m/e* 205 (M^+), 188, 177, 161, 125, 91, 77, 65. Anal. Calcd for $C_{13}H_{19}NO$ (205.29): C, 76.05; H, 9.32; N, 6.82. Found: C, 76.04; H, 9.30; N, 6.85.

α-Ethenyl-α-methyl-*N*-(2-propyl)nitrone (4fa): yield 78%. *E* isomer: oil; IR (cm^{-1}, neat) 1590 (C=N), 1150 (NO); ^1H NMR δ 1.38 (6 H, d, *J* = 6.41), 2.18 (3 H, s), 4.63 (1 H, sept, *J* = 6.41), 5.30–5.50 (2 H, m, CH_2=), 6.70–6.85 (1 H, m, –CH=); MS *m/e* 127 (M^+), 84, 68, 55, 41, 39. Anal. Calcd for $C_7H_{13}NO$ (127.18): C, 66.10; H, 10.30; N, 11.01. Found: C, 66.11; H, 10.27; N, 10.99. *Z* isomer: oil; IR (cm^{-1}, neat) 1585 (C=N), 1160 (NO); ^1H NMR δ 1.35 (6 H, d, *J* = 6.40), 2.15 (3 H, s), 4.50 (1 H, sept, *J* = 6.40), 5.50–5.70 (2 H, m, CH_2=), 7.30–7.45 (1 H, m, –CH=); MS *m/e* 127 (M^+) 84, 68, 55, 41, 39. Anal. Calcd for $C_7H_{13}NO$ (127.18): C, 66.10; H, 10.30; N, 11.01. Found: C, 66.08; H, 10.28; N, 11.04.

(*Z*)-α-Phenyl-*N*-(2-propyl)nitrone (4fb): yield 74%; oil; IR (cm^{-1}, neat) 1580 (C=N) 1145 (NO); ^1H NMR δ 1.48 (6 H, d, *J* = 6.40), 4.20 (1 H, sept, *J* = 6.40), 7.30–7.40 (3 H, m, ArH + 1 H), 8.20–8.25 (2 H, m, Ar H); MS *m/e* 163 (M^+), 162, 120, 104, 77, 65, 51. Anal. Calcd for $C_{10}H_{13}NO$ (163.21): C, 73.58; H, 8.02; N, 8.58. Found: C, 73.55; H, 8.05; N, 8.60.

(*Z*)-α-Phenyl-*N*-[1-(3-oxobutyl)]nitrone (4gb): yield 27%; oil; IR (cm^{-1}, neat) 1580 (C=N), 1160 (NO); ^1H NMR δ 2.10 (3 H, s), 3.20 (2 H, t, *J* = 7.05), 4.05 (2 H, t, *J* = 7.05), 7.30–7.35 (3 H, m, ArH + 1 H), 8.15–8.18 (2 H, m, ArH); MS *m/e* 191 (M^+), 190, 174, 143, 103, 89, 77, 65. Anal. Calcd for $C_{11}H_{13}NO$ (175.22): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.10; H, 6.86; N, 7.34.

(*Z*)-α-(2-Oxopropyl)-*N*-benzylnitrone (5gb): yield 43%; oil; IR (cm^{-1}, neat) 1590 (C=N), 1155 (NO); ^1H NMR δ 2.10 (3 H, s), 3.35 (2 H, d, *J* = 6.20), 4.90 (2 H, s), 6.62 (1 H, t, *J* = 6.20), 7.30–7.35 (5 H, m, ArH); MS *m/e* 191 (M^+), 173, 143, 91, 77, 65. Anal. Calcd for $C_{11}H_{13}NO$ (175.22): C, 69.09; H, 6.85; N, 7.32. Found: C, 69.07; H, 6.85; N, 7.29.

α-Ethenyl-α-methyl-*N*-[1-(2-furyl)-2-ethyl]nitrone (4ha): yield 21%. *E* isomer: oil; IR (cm^{-1}, neat) 1600 (C=N), 1145 (NO); ^1H NMR δ 2.17 (3 H, s), 3.22 (2 H, t, *J* = 7.02), 4.23 (2 H, t, *J* = 7.00), 5.25–5.45 (2 H, m, CH_2=), 6.40–6.55 (1 H, m, –CH), 6.05–6.10 (1 H, m), 6.25–6.30 (1 H, m), 7.26–7.30 (1 H, m); MS *m/e* 179 (M^+), 163, 154, 94, 66, 55, 41. Anal. Calcd for $C_{10}H_{13}NO_2$ (179.21): C, 67.02; H, 7.31; N, 7.81. Found: C, 67.01; H, 7.37; N, 7.84. *Z* isomer: oil; IR (cm^{-1}, neat) 1600 (C=N), 1150 (N-O); ^1H NMR δ 2.07 (3 H, s), 3.22 (2 H, t, *J* = 7.03), 4.17 (2 H, t, *J* = 7.05), 5.55–5.75 (2 H, m, CH_2=), 6.05–6.10 (1 H, m, –CH=), 6.25–6.30 (1 H, m), 7.20–7.30 (2 H, m); MS *m/e* 179 (M^+), 163, 150, 94, 82, 66, 55, 41. Anal. Calcd for $C_{10}H_{13}NO_2$ (179.21): C, 67.02; H, 7.31; N, 7.81. Found: C, 67.00; H, 7.29; N, 7.83.

(*Z*)-α-(2-Furylmethyl)-*N*-[3-(1-butenyl)]nitrone (5ha): yield 40%; oil; IR (cm^{-1}, neat) 1595 (C=N), 1145 (NO); ^1H NMR δ 1.55 (3 H, d, *J* = 6.75), 3.87 (2 H, d, *J* = 6.90), 4.40–4.50 (1 H, m), 5.20–5.35 (2 H, m, CH_2=), 6.05–6.10 (1 H, m), 6.35 (1 H, t, *J* = 6.90), 6.40–6.55 (1 H, m), 7.25–7.30 (1 H, m); MS *m/e* 179 (M^+), 163, 124, 94, 81, 55, 39. Anal. Calcd for $C_{10}H_{13}NO_2$ (179.21): C, 67.02; H, 7.31; N, 7.81. Found: C, 66.99; H, 7.29; N, 7.80.

(*Z*)-α-Phenyl-*N*-[1-(3-chlorobutyl)]nitrone (4ib): yield 30%; oil; IR (cm^{-1}, neat) 1590 (C=N), 1165 (NO); ^1H NMR δ 1.40 (3 H, d, *J* = 7.10), 2.05–2.20 (2 H, m), 3.92 (2 H, t, *J* = 7.20), 4.60–4.75 (1 H, m), 7.38–7.42 (3 H, m, ArH + 1 H), 8.15–8.20 (2 H, m, ArH); MS *m/e* 146, 102, 77, 65, 51. Anal. Calcd for $C_{11}H_{14}ClNO$ (211.68): C, 62.41; H, 6.66; N, 6.61. Found: C, 62.38; H, 6.69; N, 6.59.

(*Z*)-α-[1-(2-Chloropropyl)]-*N*-benzylnitrone (5ib): yield 45%; oil; IR (cm^{-1}, neat) 1590 (C=N), 1160 (NO); ^1H NMR δ 1.40 (3 H, d, *J* = 7.20), 2.10–2.40 (2 H, m), 4.65–4.80 (3 H, m), 6.60 (1 H, t, *J* = 5.65), 7.35–7.40 (5 H, m, ArH); MS *m/e* 186, 184, 102, 91, 77, 65, 51. Anal. Calcd for $C_{11}H_{14}ClNO$ (211.68): C, 62.41; H, 6.66; N, 6.61. Found: C, 62.44; H, 6.68; N, 6.59.

α-Ethenyl-α-methyl-*N*-[4-(2-oxopentyl)]nitrone (4ja): yield 70%. *E* isomer: oil; IR (cm^{-1}, neat) 1595 (C=N), 1160 (NO); ^1H NMR δ 1.45 (3 H, d, *J* = 6.30), 1.75–1.85 (2 H, m), 2.05 (3 H, s), 2.10 (3 H, s), 2.40–2.55 (2 H, m), 4.05–4.15 (1 H, m), 5.30–5.45 (2 H, m, CH_2=), 6.65–6.75 (1 H, m, –CH=); MS *m/e* 183 (M^+), 146, 99, 81, 55, 43, 41. Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.56; H, 9.32; N, 7.61. *Z* isomer: oil; IR (cm^{-1}, neat) 1600 (C=N), 1160 (NO); ^1H NMR δ 1.40 (3 H, d, *J* = 6.30), 1.75–1.85 (2 H, m), 2.05 (3 H, s), 2.10 (3 H, s), 2.40–2.55 (2 H, m), 4.05–4.15 (1 H, m), 5.50–5.70 (2 H, m, CH_2=), 6.30–6.35 (1 H, m, –CH=); MS *m/e* 183 (M^+), 146, 99, 81, 55, 43, 41. Anal. Calcd for $C_{10}H_{17}NO_2$ (183.25): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.53; H, 9.33; N, 7.65.

(Z)-α-Phenyl-*N*-[4-(2-oxopentyl)]nitrone (4jb): yield 71%; oil IR (cm^{-1}, neat) 1595 (C=N), 1150 (NO); ^1H NMR δ 1.48 (3 H, d, *J* = 6.30), 1.75–1.90 (2 H, m), 2.10 (3 H, m), 2.40–2.55 (2 H, m), 4.05–4.10 (1 H, m), 7.35–7.40 (3 H, m, ArH + 1 H), 8.20–8.25

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(2 H, m, ArH); MS *m/e* 219 (M^+), 218, 202, 165, 104, 89, 77, 65, 43. Anal. Calcd for $C_{13}H_{17}NO_2$ (219.28): C, 71.20; H, 7.81; N, 6.38. Found: C, 71.21; H, 7.80; N, 6.40.

α-Ethenyl-α-methyl-*N*-[4-(1-methyl-4-methoxy-4-oxobutyl)]nitrone (4ka): yield 69%. *E* isomer: oil; IR (cm^{-1}, neat) 1595 (C=N), 1160 (NO); ^1H NMR δ 1.40 (3 H, d, *J* = 6.35), 1.80–1.85 (1 H, m), 2.05–2.20 (3 H, m), 2.25 (3 H, s), 3.65 (3 H, s), 4.70–4.75 (1 H, m), 5.35–5.55 (2 H, m, CH_2=), 6.75–6.85 (1 H, m, –CH=); MS *m/e* 199 (M^+), 182, 168, 115, 96, 73, 59, 55, 41. Anal. Calcd for $C_{10}H_{17}NO_3$ (199.25): C, 60.28; H, 8.60; N, 7.03. Found: C, 60.25; H, 8.59; N, 7.04. *Z* isomer: oil; IR (cm^{-1}, neat) 1595 (C=N), 1155 (NO); ^1H NMR δ 1.43 (3 H, d, *J* = 6.30), 1.75–1.85 (1 H, m), 2.05 (3 H, s), 2.10–2.15 (3 H, m), 3.62 (3 H, s), 4.45–4.55 (1 H, m), 5.55–5.70 (2 H, m, CH_2=), 7.35–7.45 (1 H, m, –CH=); MS *m/e* 199 (M^+), 182, 168, 115, 96, 73, 59, 55, 41. Anal. Calcd for $C_{10}H_{17}NO_3$ (199.25): C, 60.28; H, 8.60; N, 7.03. Found: C, 60.25; H, 8.59; N, 7.05.

(*Z*)-α-Phenyl-*N*-[4-(1-methyl-4-methoxy-4-oxobutyl)]nitrone (4kb): yield 66%; oil; IR (cm^{-1}, neat) 1600 (C=N), 1160 (NO); ^1H NMR δ 1.50 (3 H, d, *J* = 6.30), 1.85–2.00 (1 H, m), 2.25–2.45 (3 H, m), 3.65 (3 H, s), 4.10–4.25 (1 H, m), 7.38–7.43 (3 H, m, ArH + 1 H), 8.20–8.25 (2 H, m, ArH); MS *m/e* 235 (M^+), 234, 218, 204, 132, 115, 77, 65, 59. Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.95. Found: C, 66.35; H, 7.26; N, 5.95.

(*Z*)-α-2-Propyl-*N*-benzylnitrone (5lb): yield 75%; mp 52 °C (from hexane); IR (cm^{-1}, KBr) 1590 (C=N), 1155 (NO); ^1H NMR δ 1.09 (6 H, d, *J* = 6.96), 3.10–3.20 (1 H, m), 4.85 (2 H, s), 6.48 (1 H, d, *J* = 7.12), 7.38–7.43 (5 H, m, ArH); MS *m/e* 177 (M^+), 161, 160, 91, 77, 65, 51. Anal. Calcd for $C_{11}H_{15}NO$ (177.24): C, 74.53; H, 8.53; N, 7.90. Found: C, 74.50; H, 8.56; N, 7.88.

α-Ethenyl-α-methyl-*N*-benzylnitrone (4ma): yield 16%. *E* isomer: oil; IR (cm^{-1}, neat) 1590 (C=N), 1140 (NO); ^1H NMR δ 2.15 (3 H, s), 4.85 (2 H, s), 5.30–5.45 (2 H, m, CH_2=), 6.00–6.15 (1 H, m, –CH=), 7.40–7.45 (5 H, m, ArH); MS *m/e* 175 (M^+), 145, 121, 104, 91, 77, 55, 41. Anal. Calcd for $C_{11}H_{13}NO$ (175.22) C, 75.40; H, 7.47; N, 7.99. Found: C, 75.40; H, 7.49; N, 7.98. *Z* isomer: oil; IR (cm^{-1}, neat) 1585 (C=N), 1155 (NO); ^1H NMR δ 2.28 (3 H, s), 4.85 (2 H, s), 5.50–5.70 (2 H, m, CH_2=), 6.95–7.10 (1 H, m, –CH=), 7.35–7.50 (5 H, m, ArH); MS *m/e* 175 (M^+), 145, 121, 104, 91, 77, 55, 41. Anal. Calcd for $C_{11}H_{13}NO$ (175.22): C, 75.40; H, 7.47; N, 7.99. Found: C, 75.42; H, 7.45; N, 7.96.

(*Z*)-α-Phenyl-*N*-[3-(1-butenyl)]nitrone (5ma): yield 64%; oil; IR (cm^{-1}, neat) 1590 (C=N), 1140 (NO); ^1H NMR δ 1.64 (3 H, d, *J* = 6.70), 4.55–4.60 (1 H, m), 5.30–5.40 (2 H, m, CH_2=), 6.13–6.25 (1 H, m, –CH=), 7.40–7.45 (3 H, m, ArH + 1 H), 8.21–8.25 (2 H, m, ArH); MS *m/e* 175 (M^+), 145, 121, 104, 77, 65, 55, 41. Anal. Calcd for $C_{11}H_{13}NO$ (175.22): C, 75.40; H, 7.47; N, 7.99. Found: C, 75.43; H, 7.44; N, 8.01.

Synthesis of Isoxazolidine by Cycloaddition of α-Ethenyl-*N*-(2-methylphenyl)nitrone. The reaction of 2-methylnitrobenzene (**11**) (0.685 g, 5 mmol) and allylmagnesium bromide (**12**) (5.5 mmol, 4.6 mL, 1.2M in THF) was performed as for the synthesis of nitrone **4bb**. The crude nitrone **13** was dissolved in THF (20 mL), and acrylonitrile (0.318 g, 6 mmol) was added. The solution was refluxed for 24 h, and evaporation of the solvent gave 2-(2-methylphenyl)-3-ethenyl-4-isoxazolidinecarbonitrile (**14**) and 2-(2-methylphenyl)-3-ethenyl-5-isoxazolidinecarbonitrile (**15**) as a nonseparable mixture of diastereomers. They have been recognized through mass spectrum analysis: *m/e* 214 (M^+), 160, 144, 118, 104, 91, 65, 39.

Reaction of 1-Nitrobutane (1d) with Alkyl Grignard Reagents. To a stirred THF solution (20 mL) of **1d** (0.515 g, 5 mmol) at –70 °C was added a solution of Grignard reagent (5.5 mmol) in THF under N_2. The mixture was stirred for 20 min and then was quenched by addition of saturated aqueous NH_4Cl and extracted with diethyl ether. The organic layer, dried over Na_2SO_4, was concentrated and submitted to flash-chromatographic purification on a silica gel column eluted with hexane–diethyl ether (9:1) to give the following product distributions.

(a) **1d** with 1-butylmagnesium bromide (**2c**): **1d** (58%), azoxybutane (28%), azobutane (3%), dibutylhydroxylamine (5%), and α-propyl-*N*-butylnitrone (2%).

(b) **1d** with 1-decylmagnesium bromide (**2d**): **1d** (46%), azoxybutane (26%), 1-decanol (46%), *n*-decane (32%), azobutane (3.5%), *N*-butyl-*N*-decylhydroxylamine (5%), and 1-decene (8%).

(c) **1d** with *tert*-butylmagnesium bromide (**2e'**): **1d** (80%) and α-propyl-*N*-*tert*-butylnitrone (15%).

All compounds were identified by comparison with authentic samples.

Isomerization of Nitrones. To a solution of nitrone (1.5 mmol) in absolute EtOH (5 mL) was added two drops of a stock solution prepared from MeONa (0.65 g, 12 mmol) and EtOH (2 mL), and the resulting solution was heated at reflux for the appropriate time. The isomerization progress was monitored by a GLC mass detector as indicated in Table II. The overall yield of the recovered material was determined by GLC analysis using an internal standard.

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