# Radical Addition to Amide-Substituted Alkenes: Stereoselective Intermolecular Radical Additions

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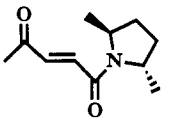
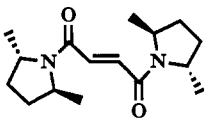
Carbon–carbon bond forming addition of radicals containing a stereogenic center to alkenes can occur with high stereoselectivity. The scope of this reaction has been explored extensively in recent years.[1] High stereoselectivities in addition reactions are usually observed from cyclic radicals bearing substituents on carbons adjacent to the radical,[2-4] and steric effects are suggested to play a dominant role in this selectivity. For example, addition to acrylonitrile of 2-methylcyclopentyl radical occurs with a selectivity of 92:8, addition of the radical occurring preferentially on the face of the ring opposite the substituent.[4] In contrast there is, to our knowledge, only one report of a stereogenic center on an acyclic alkene directing the addition of a radical to one diastereoface of the alkene,[5] and there is no general understanding of the structural requirements that might lead to high selectivities in C–C bond forming reactions of this type. Thus, extensive investigations of several chiral fumarate esters generally gave low selectivity in the addition of radicals to the fumarates,[6] and in only one case, a monomaleate ester, was significant stereoselectivity observed.[5]

In the course of our studies on radical macrocyclization,[7,8] we explored the use of alkenes bearing a chiral pyrrolidine amide as an auxiliary, and we found significant stereoselectivity in these intramolecular additions. These amide auxiliaries control the orientation of the pyrrolidine stereogenic center relative to the alkene diastereofaces (vide infra), and this serves as a steric shield for addition to one face of the alkene. This analysis applies for intermolecular additions as well as intramolecular additions, and we report here our study of two intermolecular radical additions that use this auxiliary and that proceed with high selectivity.

The two alkenes studied were both amides of 2,5-dimethylpyrrolidine, available as the *S,S* enantiomer from L-alanine.[9,10] One alkene was the unsymmetrical monoamide, **1**, derived from 4-oxo-2-pentenoic acid while the other substrate examined was the diamide, **2**, of fumaric acid. The monoamide **1** was prepared



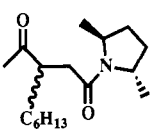
**1**



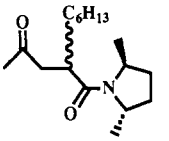
**2**

from the corresponding acid by a mixed anhydride coupling procedure while the fumarate diamide was prepared from fumaric acid via fumaric chloride. Addition of alkyl radicals was achieved by both the "tin method" involving tin hydride mediated generation of alkyl radicals and the "mercury method" that uses alkylmercuric halide/sodium borohydride or cyanoborohydride as the radical source.[1]

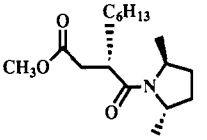
Addition of *n*-hexyl radical to **1** gives four isomeric addition products. Two of these products, **3a** and **3b**, are the result of addition of the radical to the ketone end of the alkene while two products, **4a** and **4b**, result from addition to the amide end.



**3a,b**



**4a,b**



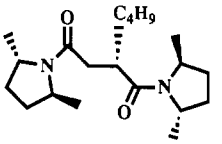
**5a**

Separation of the **4a** diastereomers was achieved by preparative HPLC on silica gel (1:1 ethyl acetate/hexane) or by capillary gas chromatography on a 30-m SPB-1 column. While NMR did not help in distinguishing the products, mass spectroscopy was useful in the identification of the **3** and **4** radical adducts.[12] The products formed by radical addition next to the ketone, **3a** and **3b**, are formed with little selectivity (60:40 product ratio) while the products **4a** and **4b** are formed in ratios as high as 93:7. Consequently the stereochemistry of these compounds was proved by structure degradation and independent synthesis.

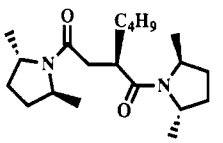
The methyl ketone functional group of the major product formed, **4a**, was converted to the succinic acid mono methyl ester (compound **5a**) by the iodoform reaction followed by diazomethane.[13,14] This stereoisomer was independently synthesized from (−)-(*S*)-2-hexylsuccinic acid by (1) formation of the (*S*)-2-hexylsuccinic anhydride by reaction with acetyl chloride, (2) conversion of the anhydride to a mixture of two regioisomeric monomethyl esters after reaction with methanol, (3) formation of the monoester–mono acid chloride by reaction with thionyl chloride, and (4) reaction of the acid chloride with 2(*S*),5(*S*)-dimethylpyrrolidine.[15]

The major product formed by addition of hexyl radical to the alkene **1** gives a methyl ester **5a** that is identical in every respect with the diastereomer synthesized independently. Thus, with the (*S,S*)-pyrrolidine auxiliary, the new stereogenic center is formed at the alkene with *S* configuration while the (*R,R*)-pyrrolidine would give a new *R* center. At 80 °C, the product distribution of alkene radical adducts is **3a,b**:**4a,b** = 1.1 and **4a**:**4b** = 7.2 while at 0 °C these ratios are **3a,b**:**4a,b** = 0.95 and **4a**:**4b** = 15.0.

When the fumaramide **2** was reacted with *tert*-butyl radical, only two isomeric radical adducts were obtained, these products differing only by the configuration at the newly formed stereogenic center. The stereoisomeric compounds **6a** and **6b** could be separated by capillary gas chromatography (SE 30, 20 m) and by flash chromatography on silica gel (pentane/acetone = 4:1).



**6a**



**6b**

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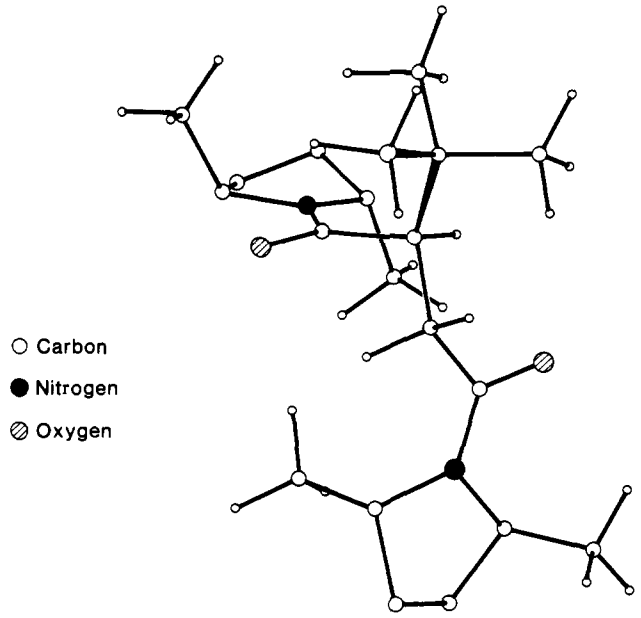


**Figure 1.** Solid-state conformation of **6a** from single-crystal X-ray analysis.

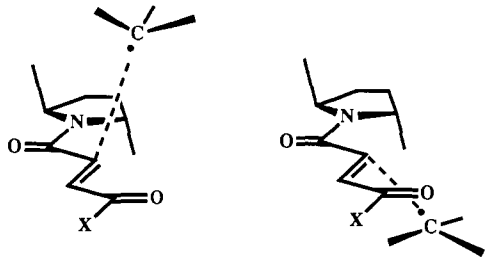


**Figure 2.** Model for radical addition to chiral alkenes.

The main isomer **6a** gave crystals (from hexane, mp = 91–92 °C), on which a single-crystal X-ray analysis was carried out.[16] The structure for isomer **6a** is presented in Figure 1, and examination of the structure indicates that the new stereogenic center has been formed with the *R* configuration. Because of the different priorities of the *n*-butyl and *tert*-butyl groups in structures **4** and **6**, the major adduct formed in the radical addition to both **1** and **2** is the result of addition from the analogous face of both alkenes (see structures **5a** and **6a**) even though the configuration of the newly formed centers is different. The ratio of products **6a**:**6b** is 16:1 at 110 °C, and at 20 °C, the ratio is **6a**:**6b** = 40:1.

The diastereoselectivity observed for radical addition to **1** and **2** can be understood by the model shown in Figure 2. The dimethylpyrrolidine auxiliary fixes the dimethyl groups of the auxiliary relative to the alkene faces by virtue of the favored conformation as shown about the carbonyl C–$C_\alpha$ bond and the $C_2$ axis of the pyrrolidine group. In fact, molecular mechanics calculations suggest that the conformation about the carbonyl C–$C_\alpha$ bond shown in Figure 2 is favored by over 3 kcal/mol over the other planar conformation possible in which the carbonyl oxygen and amide nitrogen have exchanged positions. The nucleophilic radical has a required approach to the olefin on a vector over the pyrrolidine, and this sterically protects one face of the olefin from addition. In support of the model, we note that addition of hexyl radical to the end of **1** remote from the amide occurs without significant diastereoselectivity. That steric effects are important in the selectivity observed is also suggested by the fact that the bulky *tert*-butyl radical gives higher selectivities than the smaller *n*-hexyl radical.

The observation of significant selectivities in radical additions to unsaturated amides with $C_2$ symmetry auxiliaries opens the possibility for the use of free radicals in the construction of stereogenic centers with defined configuration. The success achieved by the use of sterically hindered radicals in these additions is noteworthy since construction of structures of this type by carbanionic alkylation procedures would be particularly difficult.

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**Supplementary Material Available:** Tables of bond lengths and angles (19 pages); tables of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

(16) Space group $P2_1$; $a$ = 3.678 (10) Å; $b$ = 17.575 (10) Å; $c$ = 6.253 (5) Å; $\beta$ = 106.78 (5)°; $V$ = 1018.1 Å$^3$; $Z$ = 2; $\rho_{calcd}$ = 1.098 g cm$^{-3}$; $\mu$(Cu K$\alpha$) = 4.77 cm$^{-1}$. Tables of parameters, bond lengths and angles, and observed and calculated structure factors are available from the Cambridge Crystallographic Data File and as supplementary material.

## Oxidation of Methylhydrazine at a Metal Center. Stereoselective Synthesis of *cis*-Methyldiazene, NH=N(CH$_3$)

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We have recently reported the preparation and some aspects of the fundamental reaction chemistry of monosubstituted *cis*-aryldiazenes, *cis*-NH=NR (R = aryl group).[1,2] These are simple but significant molecules because they are often invoked as reactive intermediates in a wide range of organic transformations (that usually involve loss of dinitrogen)[3,4] and are thought to be ubiquitous reactive metabolites responsible (as alkylating agents) for the carcinogenic activity often found in molecules containing the diazo functionality.[5]

Thus far our synthetic approach, entailing the displacement of *cis*-NH=NR from [*trans*,*trans*-W(NH=NR)(CO)$_2$(NO)(PPh$_3$)$_2$$^+$][PF$_6^-$] by bromide ions, has been limited to the preparation of *aryl*diazenes because the key tungsten complex is prepared by a 1,1-insertion reaction of an aryldiazonium cation into the W–H bond of *trans*,*trans*-W(H)(CO)$_2$(NO)(PPh$_3$)$_2$ (**1**),[6] and simple non-aryl diazonium salts (RN$_2^+$, R = H, alkyl) are unstable. Herein we report that a route to *cis*-methyldiazene has been developed, involving selective oxidation of methylhydrazine coordinated to a tungsten complex, that provides the first synthetic entry to cis-monosubstituted diazenes that contain an alkyl group.

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