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COMPETITION RATE CONSTANTS FOR ADDITION OF CYCLOHEXYL RADICAL TO AMIDE SUBSTITUTED ALKENES ORIGINS OF ACYCLIC STEREOSELECTION IN RADICAL ADDITIONS

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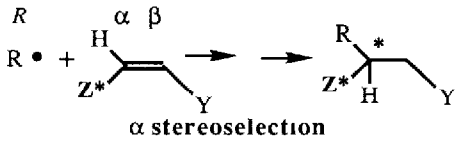
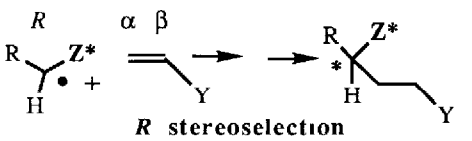
Abstract *Competition rate constants were determined for the addition of cyclohexyl radical to α,β unsaturated amides derived from pyrrolidine and trans-2,5-dimethylpyrrolidine The relative rates can be understood by single crystal X-Ray analyses of the alkenes and an examination of the presumed transition state*

The control of stereochemistry in free radical reactions has received increased attention in the past several years and significant stereochemical control has been realized for the reactions of cyclic radicals where the radical faces are differentiated by bulky groups or in cyclic alkenes where the same steric hindrance strategy is employed to differentiate olefin faces [1,2] There is less of a record of success for acyclic stereocontrol in free radical reactions and only recently has significant control of stereochemistry been demonstrated in free radical additions

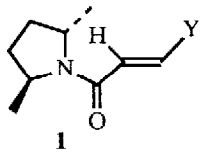


α stereoselection



R **stereoselection**

We[3-5] and Giese[5,6] have reported unprecedented α stereoselection in the addition of radicals to alkenes substituted with chiral amides prepared from 2,5-dimethylpyrrolidine Substitution of chiral amides onto a radical center also gives rise to stereoselection in the center formed from a radical (*R* stereoselection) and amides derived from 2,5-dimethylpyrrolidine are effective control elements in *R* stereoselection[7,8] as are amides of a sultam derived from camphor [9] Thus, stereoselective radical addition reactions have been achieved with alkenes



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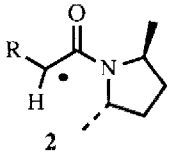

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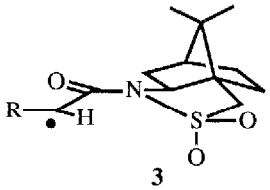


3

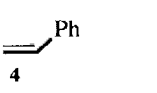
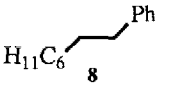
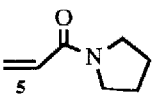
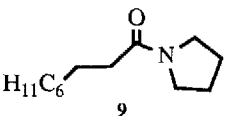
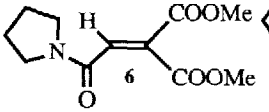
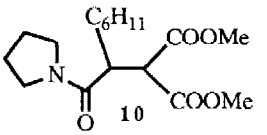
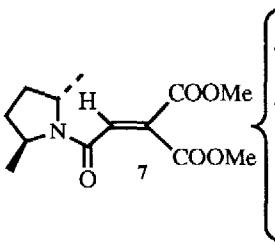
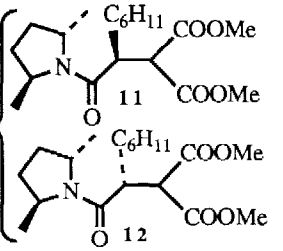
substituted as in **1** or from radicals like **2** or **3**

While we have made proposals about the origins of the observed α selectivity based upon models of preferred conformations of the alkene,[5,10] experimental support for these models is lacking and additional data

concerning these first-generation auxiliary systems is required We report here competition kinetic and structural data that are relevant to the question of acyclic stereocontrol from pyrrolidine-amide auxiliaries and we present an analysis of this auxiliary that may provide a point of reference for other systems

Cyclohexyl radical, generated from borohydride reduction of cyclohexylmercuric acetate, was added to the alkenes **4-7** and the products of addition, **8-12**, were fully characterized [11,12] Competition kinetics experiments were carried out at 22±1 °C [13] Each alkene pair was examined in competition in at least three different concentration ratios and the alkenes were always present in at least a 10-fold excess relative to the radical precursor Product mixtures were analyzed on a 30 m SPB-5 capillary column and the detector responses of all addition products were determined by analysis of standard mixtures Table 1 presents the relative rate constants compared to dimethylfumarate (k_{rel}=1 0) for the alkenes studied

Table 1. *Competition Rate Constants For Addition of Cyclohexyl to Alkenes **4-7** Relative to Dimethyl Fumarate*

Reactant	*Product*	k_{rel}	k_{rel} *(statistically corrected)* [a]
		7 7±0 6 • 10^{-3}	1 5±0 1 • 10^{-2}
		3 4±0 1 • 10^{-2}	6 8±0 1 • 10^{-2}
		0 36±0 01	0 72±0 02
		0 23±0 01	0 92±0 02
		0 009±0 001	0 037±0 003

a Dimethyl fumarate has 4 equivalent addition sites while **4**,**5**, and **6** have two equivalent sites and **7** has two inequivalent sites

Single crystal X-ray analysis of the alkenes **6** and **7** was carried out[14] and their solid state structures are shown in Figure 1 Both alkenes adopt similar conformations of amide relative to the double bond The amide

carbonyl oxygen is in a "Z" orientation with respect to the olefin for both compounds while torsion angles about the alkene-amide carbonyl and amide carbonyl-pyrrolidine nitrogen are somewhat distorted Thus, C=C(H)-C(O)-N and C(H)-C(O)-N-C are +164 3(2)° and -3 5(3)°, -178 3(2)° for **6** while analogous torsion angles for **7** are -173 7(2)° and +10 5(3)°, -172 2(2)° The pyrrolidine is in a half-chair conformation for both **6** and **7** and the methyl substituents of **7** occupy pseudo-axial positions The observed solid state conformation for **7** is close to

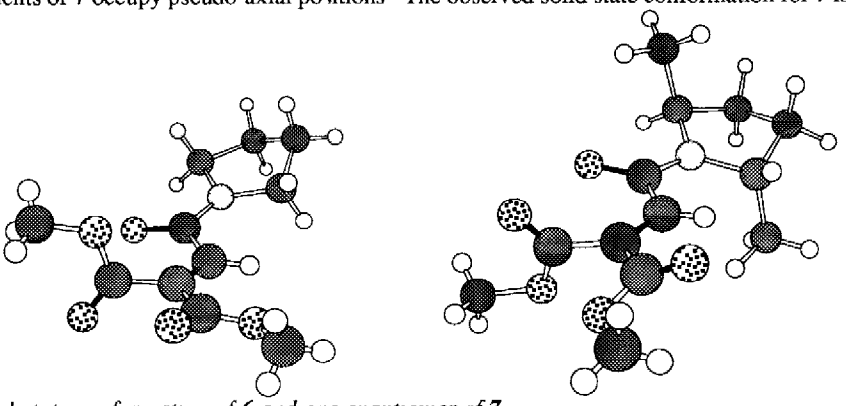


Figure 1. *Solid-state conformation of* ***6*** *and one enantiomer of* ***7***

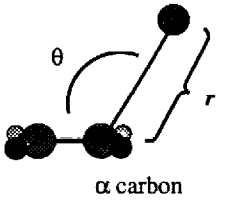
the structure predicted by molecular mechanics [5,10]

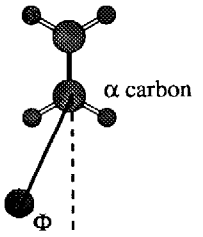
The amide group is an activating group for alkenes in their reactions with nucleophilic radicals Thus, **5**, being some 4 5 times more reactive than styrene, is somewhat less reactive than acrylate esters towards addition of cyclohexyl radical On the other hand, alkenes such as **6** or **7** that are substituted with the amide group and with two vicinal esters, are nearly as reactive as dimethyl fumarate towards addition

Comparison of the relative rates of addition for **6** and **7** is particularly instructive Addition to the face of **7** that leads to the minor product of addition, **12**, occurs with a relative rate 20 times less than addition to the model alkene **6** Addition of cyclohexyl to the face of **7** that leads to the major product **11** occurs with a rate *~1 3 times greater* [15] than addition occurs to the model alkene **6** The methyl substituents on the pyrrolidine protect one face of the alkene from addition while modestly activating the alkene toward addition from the opposite face

The orientation of the pyrrolidine methyl substituents are critical to the selectivity and consideration of the polar coordinates of such protecting groups relative to the α carbon provides a reasonable framework for evaluation of potential auxiliaries The distance of groups from the α carbon, *r*, and the two angles Φ and θ as shown below are important parameters for evaluation of selectivity We suggest that groups which occupy a volume of space with coordinate Φ ~ 0 °, θ ~ 110 °and with a small *r* value (2 5-4 0 Å) protect electrophilic

alkenes from addition of nucleophilic radicals [16] For the alkene **7**, the pyrrolidine methyl that protects the bottom face from addition (Figure 1) has coordinates of r = 3 34, Φ = 10 8 °, and θ = 141° while the top face of **7** is relatively accessible, methyl coordinates, r = 4 35, Φ = 60 °, and θ = 157° Analogous coordinates may prove to





be useful in discussions of *R* stereoselection

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11 All new compounds were fully characterized by spectroscopy and elemental analysis

12 Known compounds were prepared by established literature procedures and gave spectra consistent with the proposed structures

13 Giese, B , *Angew Chem , Int Ed Engl* , 1983, 22, 753 and references cited therein An analogous competition kinetics approach has been developed for stereoselective dipolar cycloadditions, Curran, D P , Heffner, T A , *J Org Chem* , 1990, 55, 4585

14 *Crystal data* **6**, $C_{11}H_{15}NO_5$, monoclinic, space group $P2_1/c$, a = 9 922(1) Å, b = 8 197(1) Å, c = 15 989(1) Å, β = 110 56(1)° (from 25 orientation reflections, 42°<θ<48°), V = 1217 6 (4) Å^3, Z = 4, D_C = 1 316 g cm^{-3}, μ (Cu-$K\alpha$ radiation, λ = 1 5418 Å) = 8 4 cm^{-1}, crystal size 0 30x 0 30 x 0 50 mm, (±)-**7**, $C_{13}H_{19}NO_5$, monoclinic, space group $P2_1/c$, a = 10 425(1) Å, b = 8 698(1) Å, c = 16 030(2) Å β = 90 90(1)° (from 25 orientation reflections, 41°<θ<48°), V = 1453 4 (5) Å^3 Z = 4, D_C = 1 231 g cm^{-3}, μ (Cu-$K\alpha$ radiation = 7 5 cm^{-1}, crystal size 0 30x 0 30 x 0 30 mm
Intensity data ($+h$, $+k$, $\pm l$, 2644 refls , θ_{max} = 75°) were recorded on an Enraf-Nonius CAD-4 diffractometer [Cu-$K\alpha$ radiation, graphite monochromator, ω–2θ scans, scanwidth (0 90 + 0 14tanθ)°] From totals of 2350(**6**) and 2990(**7**) non-equivalent measurements, those 1829 and 2206 reflections with I>3 0σ(I) were retained for the analyses Initial coordinates for all non-hydrogen atoms were obtained from *E*-maps (MULTAN11/82) Hydrogen atoms were located in difference Fourier syntheses Full-matrix least-squares refinement (anisotropic C, N, O, isotropic H) converged (max shift/esd = 0 03) at R = 0 049 (R_W = 0 067) for **6** and R = 0 042 (R_W = 0 058) for **7** Atomic parameters, bond lengths, and angles have been deposited at the Cambridge Data Centre

15 The enhanced reactivity of **7** compared to **6** may be due to distortion of the amide structure Twisting about the C-N bond would reduce resonance delocalization of the carbonyl and make the amide group more electron withdrawing The apparent reason for increased distortion about the amide linkage of **7** is the steric crowding of the vinylic C-α hydrogen and the pyrrolidine methyl

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