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The Regiochemistry and Stereochemistry of 1,3-Dipolar Cycloadditions of 1-Fluoro- and 1,1-Difluoroallene

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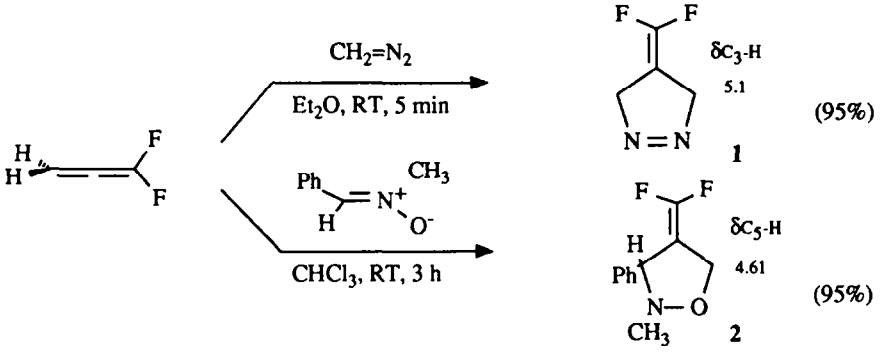
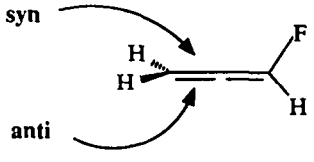
Abstract: 1,3-Dipolar cycloadditions of diazoalkanes, nitrones and nitrileoxides occur with high regioselectivity to 1,1-difluoroallene and fluoroallene, and with variable syn or anti π-facial diastereoselectivity with regard to additions to the latter. The roles of steric effects, frontier molecular orbital effects, electrostatic interactions and other factors which may be involved in determining the observed regioselectivity and π-facial diastereoselectivity are discussed.

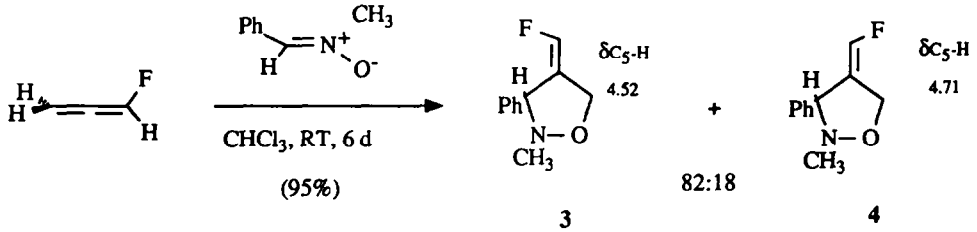
1,1-Difluoroallene, (**DFA**), undergoes facile, high-yield, and totally regiospecific cycloaddition to its C_2 - C_3 double bond with 1,3-dipolar reagents such as diazo compounds, nitrones, nitrileoxides and carbonyl ylides.[1,2] Its reactions with diazomethane and N-methyl-C-phenylnitrone provide typical examples:



Fluoroallene, (**MFA**), is likewise regiospecific its cycloadditions with 1,3-dipoles, but unlike **DFA**'s reactions, there is a stereochemical element in **MFA**'s cycloadditions, in that addition to the C_2 - C_3 bond can



occur from either the side *syn* to the fluorine substituent or *anti* to it, as depicted above. Indeed, it has been found that for typical cycloadditions of nitrones with **MFA**, there is a pronounced favoring of syn addition:[3,4]



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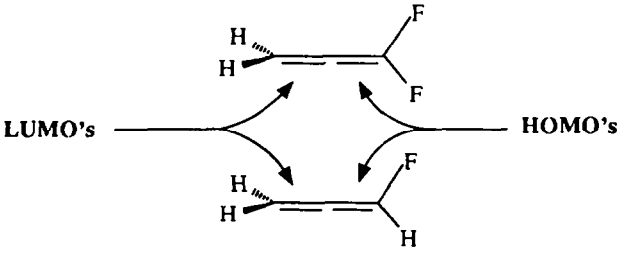
The assignments of syn and anti stereochemistry for these and all other cycloaddition adducts reported in this paper are based upon various previously reported features of the nmr's of the respective syn and anti adducts.[3,4] For example, there are slightly larger *trans*-allylic than *cis*-allylic H-H coupling constants observed between the vinyl C*H*F proton and the formerly allenic CH_2 protons. More significantly, these CH_2 protons are always more highly deshielded when the vinylic fluorine substituent is syn to them.(Throughout this paper, the pertinent chemical shifts are included in the reaction schemes for easy comparison.) Such structural correlations were verified via an x-ray structure determination for the syn adduct of N-methyl-C-naphthylnitrone to **MFA**.[3]

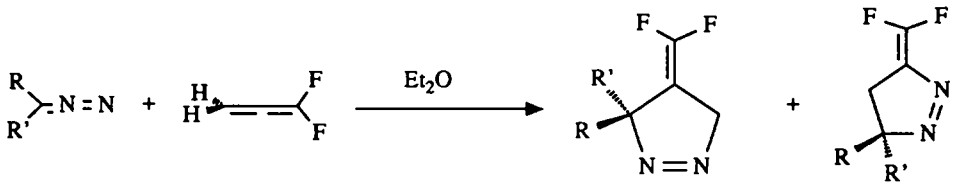
According to a perturbation theory analysis of molecular interactions,[5,6] *three* forces are potentially operative in the determination of the regio- and stereochemistry of bonding in any cycloaddition reaction: (1) electron density on one reactant interacting repulsively with that on the other (nonbonded, steric repulsion); (2) occupied molecular orbitals on one reactant mixing with unoccupied orbitals on the other (frontier MO interactions); (3) atoms in one reactant with net positive charge attracting atoms in the other with net negative charge and repelling atoms with net positive charge (electrostatic interaction). The importance of molecular orbital interactions in determining reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions has been discussed in a very important paper by Houk, [7] while the potential significance of electrostatic interactions in the determination of regiochemistry of concerted cycloaddition reactions, specifically Diels-Alder reactions, has been discussed in a recent series of papers by Hehre.[8-10]

In the case of **DFA** and **MFA**, both empirical and ab initio molecular orbital calculations indicate their LUMO's to be localized in their C_2-C_3 π^* orbitals.[11-13] Thus it is reasonable to expect allowed, concerted



cycloadditions, such as our observed 1,3-dipolar cycloadditions, to take place preferentially with these bonds. These same calculations indicate, however, that the LUMO coefficients at C_2 and C_3 for both allenes are not significantly different, and thus cannot readily explain the observed regiospecificity of the cycloadditions with respect to the orientation of the 1,3-dipoles.

Indeed, it was found that when substituted diazo compounds (**5a-c**) underwent reaction with **DFA**, *both* possible orientations for addition of the diazo species were observed.[1] The formation of regioisomers of



5-a R = R' = Me

b R = R' = fl =

c R = R' = Ph

6-a,b,c

	δC_5-H
a	5.19
b	5.65
c	5.34

7-a,b,c

δC_5-H

2.1

2.42

3.02

Table I. Regiochemistry of Diazoalkane Cycloadditions to **DFA**[1]

		Relative Yield Regioisomers		
Diazoalkane	Conditions	6	7	Total Yield
$CH_2=N_2$	RT, 5 min	>99	-	95%
5-a	0°, 5 min	61	39	99
5-b	RT, 4 h	28	72	99
5-c	28°, 5 h	14	86	95

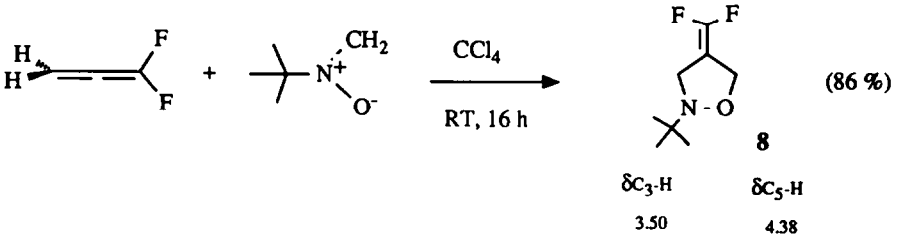
alternate structure **7** was attributed to the intervention of steric effects, that is the interaction of the diazoalkane substituents with the $C=CF_2$ end of the **DFA** skeleton.

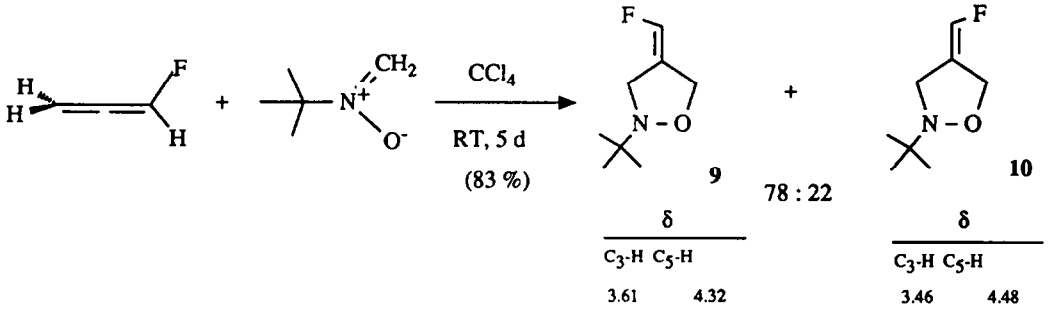
In this paper, we wish to present additional results on the regio- and stereochemistry of 1,3-dipolar cycloadditions of 1,1-difluoroallene and fluoroallene, results which provide potential insight into the factors which give rise to such selectivity.

Results

Nitrones. In all examples thus far studied, a *single* regioisomeric product has been obtained in the addition of nitrones to either **DFA** or **MFA**. Therefore, whatever interaction is giving rise to this effect does not appear to be affected by substituents at C or N of the nitrone. Nevertheless, in order to more fully evaluate the effect of substituents on C, and to provide a good model system for calculations, the

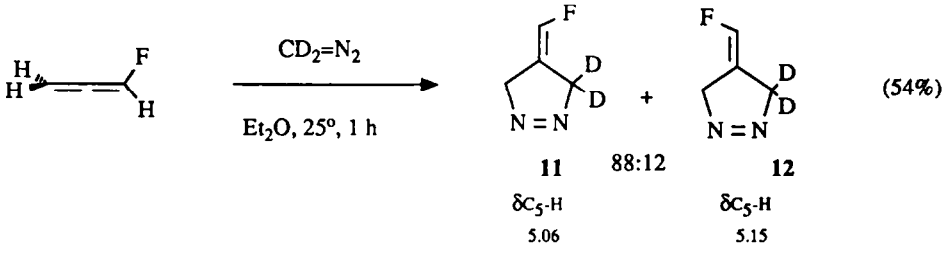
cycloadditions of N-t-butylnitrone[14] to **DFA** and **MFA** were carried out. As one can see, the results mimiced closely those of the more highly substituted nitrones, with a completely regiospecific addition to both **DFA** and **MFA**, and a stereoselective addition to **MFA** with an observed syn/anti ratio of 3.6..





Diazo Compounds. The above-described, earlier-reported results on the cycloadditions of diazo compounds with **DFA**[1], summarized in Table I, indicated that substituents on the diazo compounds gave rise to increasing proportions of regioisomer **7** as the substituents became bulkier.

Cycloadditions of these same diazo compounds with **MFA** gave rise to even more insightful results. For example, the reaction of dideuteriodiazomethane resulted in the most stereoselective cycloaddition to **MFA** which we have yet observed, with a syn/anti ratio of 7.3 being obtained. In studies of the substituted



diazo compounds, not only does the regioisomer (**13** + **14**) analogous to **7** become predominant as the substituents become bulkier, but the *anti* stereoisomer **14** also is seen to predominate for this regioisomer.Table II summarizes the results. As was the case for the counterpart **DFA** adducts[1], **MFA** adducts **11-b** & **c** and **12-b** & **c** were found to be unstable to the reaction conditions, and deazetized to form methylenecyclopropanes **15-b** & **c** and **16-b** & **c**. While there is no reason to expect that the stereochemistry

of the vinylic fluorine should have been modified during the process of formation of the

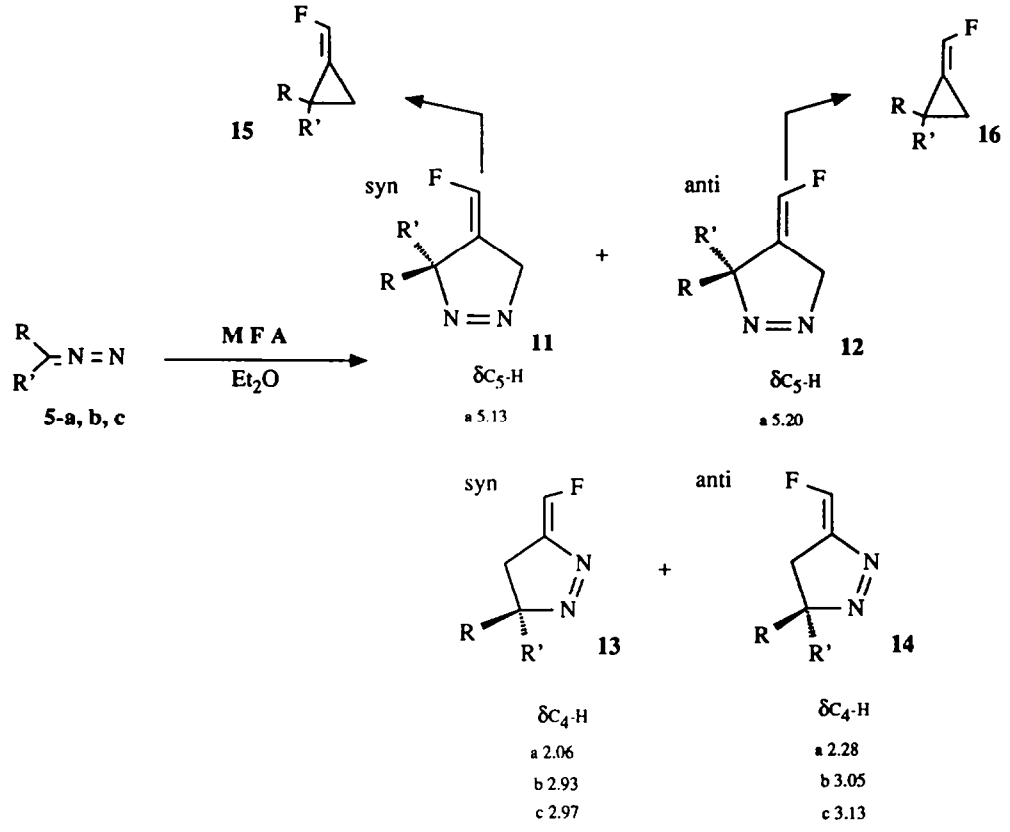


Table II. Regio- and Stereochemistry of Diazoalkane Cycloadditions to **MFA**

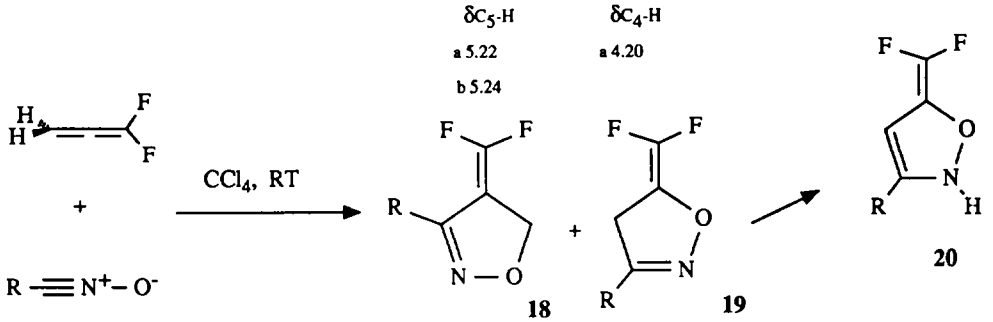
Diazo Alkane	Conditions	Relative Yields of Products 11	12	13	14	Regioisomeric Ratio	Total Yield
$CD_2=N_2$	RT, 1 h	88%	12%	-	-	∞	54%
5-a	RT, 5 min	37.8	23.3	4.2	34.7	10.5	92
5-b	RT, 48 h	11.2[a]	20.6[b]	8.8	59.3	0.46	98
5-c	RT, 2-3 wk	2.7[c]	6.9[d]	8.9	81.5	0.11	94

[a]actually observed and isolated **15-b**; [b]**16-b**; [c]**15-c**; [d]**16-c**

methylenecyclopropanes, in lieu of direct evidence to that effect, one cannot say anything definite about the

ratio of adducts **11-a & b** and **12-a & b**.

Nitrile Oxides. The results from cycloaddition of phenylnitrileoxide and mesitylnitrileoxide to both **DFA** and **MFA** are given below and in Table III. An interesting observation is the formation of alternate regioisomer **19** in the reaction of **DFA** with phenyl- but not mesitylnitrileoxide. Regioisomer **19** was found to rearrange slowly via prototropic shift to its isomer **20**.



17-a	R = Phenyl	1 h (75%)	56%	44%
-b	R = Mesityl	12 h (94%)	>99	-

In both nitrile oxide cycloadditions to **MFA**, anti addition was found to predominate:.

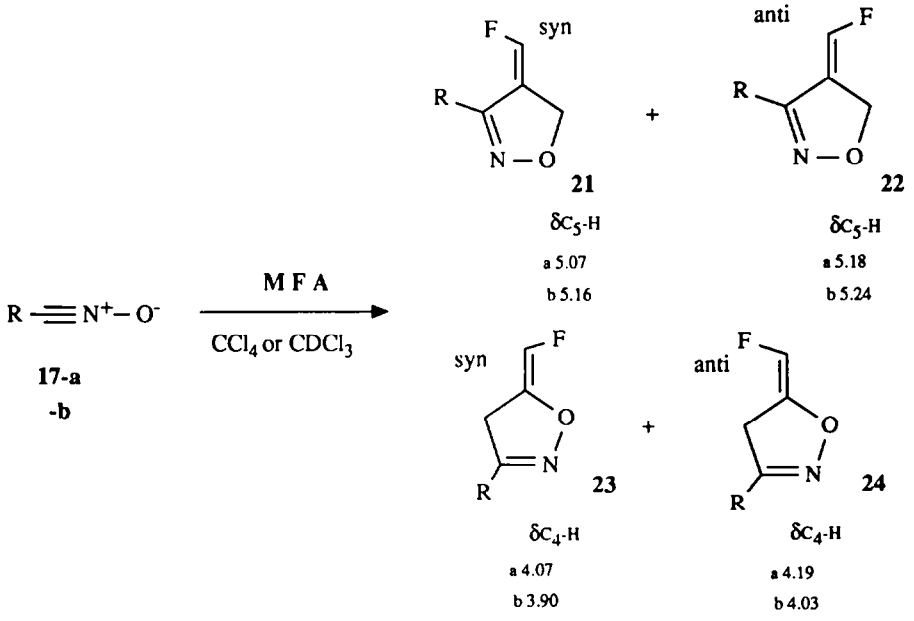


Table III. Regio- and Stereochemistry of Nitrileoxide Cycloadditions to **MFA**

Nitrile Oxide	Conditions	Relative Yields of Products 21	22	23	24	Regioisomeric Ratio	Total Yield
17-a	-10°, 10 h	4.0	35.8	16.7	43.5	0.65	88%
17-b	-10°, 24 h	4	85	4	7	8.1	93

General Discussion.

Regioselectivity- In evaluating the various possible sources of consequential interaction, we conclude that simple frontier molecular orbital effects[7] are probably not primarily responsible for the determination of the *regio*chemistry of 1,3-dipolar cycloadditions to **DFA** and **MFA**. The main reason for this conclusion lies in the almost total *lack* of regioselectivity which is observed in the Diels-Alder reactions of **DFA**. For example, in the cycloaddition of 2-(trimethylsiloxy)-1,3-butadiene with **DFA**, equal amounts of the two regioisomeric Diels-Alder adducts are obtained,[15] this in spite of the fact that the coefficients at C_1 and C_4 of this diene are considerably different (approx. 0.352 vs 0.103, respectively)[8]. In contrast, cycloadditions of non-sterically-obtrusive 1,3-dipoles, such as diazomethane, with **DFA** occur with total regiospecificity in spite of the fact that the coefficients of the termini of diazomethane's HOMO are much less disparate (i.e., 0.775 vs 0.626)[16] than those of the diene. In essence, the relative lack of regioselectivity in Diels-Alder reactions of **DFA** with unsymmetrically substituted dienes having significantly different HOMO coefficients at C_1 and C_4 would seem to speak strongly against frontier molecular orbital effects being determinant in the highly regioselective reactions of **DFA** with 1,3-dipoles which have less disparate terminal HOMO coefficients.

Steric effects may well play a role in reversing the orientational preference observed in the addition of diazomethane to **DFA** and **MFA** when bulkier substituents than hydrogen are on the carbon (as discussed above). However, in the addition of nitrones the single observed orientation of addition is clearly contrary to what would be expected on the basis of steric effects, and the trends seen in the regiochemical results for the nitrileoxide cycloadditions cannot be rationalized simply on the basis of steric effects.

While there doesn't seem to be any clear cut MO or steric effect explanation for the regiochemical outcome of these reactions, electrostatic potential interactions may in the end provide a reasonable rationale. Electrostatic interactions essentially reflect the first-order coulombic interactions of charged or polar reactants. The interaction "energy" is the energy arising from attraction or repulsion of the net partial charges associated with each atom in the transition state. Depending upon the charge and orientation of the reactants, the electrostatic energy may be negative (a net attractive interaction) or positive (a net repulsive interaction). In a reaction such as a 1,3-dipolar cycloaddition, all other things being equal (which they seem to be as far as steric and orbital considerations are concerned), one would expect the electrostatic dipoles to be preferentially oriented so that opposite charges on the interacting reactants would be adjacent to each other. Electrostatic interactions between polar molecules are important both because they dominate at long distances and because they are large in the transition state region. Clearly an evaluation of the electrostatic interaction energy is essential to the

interpretation of all reactions of polar species.

Indeed, preliminary calculations of electrostatic potentials for **DFA** and the nitrone model $CH_2=NH^+-O^-$ indicate that the negative ends of these molecules are the CF_2 end of the allene and the O atom of the nitrone,[17] and the favored approach of the two reactants towards a reaction transition state was found to be that which would lead to that single regioisomer which is observed in all of the nitrone cycloadditions of **DFA** and **MFA**.[17]

At this point the analogous predictions with respect to the cycloaddition reactions of diazo compounds or nitrile oxides are not clear, although preliminary calculations are, for example, not inconsistent with products **1** and **8** deriving from electrostatically-favored transition states. There actually seems to have been nothing yet published regarding the influence of electrostatic potential interactions in 1,3-dipolar cycloadditions.[18]

π-Facial Diastereoselectivity - Similar factors should come into play in determining the favored approach of the 1,3-dipole to either the syn or the anti C_2-C_3 π face of **MFA**. Any preference for syn addition is of course by its nature contrary to any possible steric effect which might be exerted by the fluorine substituent. Moreover, there are no documented examples of a single fluorine substituent giving rise to a steric inhibition of a reaction. Therefore, steric effects, due to the fluorine substituent, are not considered important as a determining factor for the stereochemical results observed in our 1,3-dipolar cycloadditions of **MFA**.

According to the above-mentioned analysis,[17] the electrostatic interaction of the nitrone's O with **MFA**'s CH_2 carbon will be favorable from either syn or anti approach. However the electrostatic interaction of the nitrone CH_2 carbon with **MFA**'s F substituent would be favorable for the hypothetical syn π-facial approach, while there would be no such favorable interaction in the hypothetical anti approach. Therefore, there seems to be the potential that analyses of electrostatic interactions will be able to be used generally to rationalize the syn π-facial preference for 1,3-dipolar cycloadditions to **MFA**.

Examining the data for diazoalkane addition to **MFA** more specifically, one can rationalize the change in *regio*chemistry on the basis of an increase in steric repulsion in going from diazomethane to the substituted diazoalkanes, **5-a** to **5-c**, much as we did in the **DFA** reactions. In addition, assuming that increasing the steric bulk of the diazoalkane should exacerbate any steric effect difference between H and F (could this be an example of a weak *F* steric effect?), one can even explain the observed decreasing syn selectivity for this regioisomer. As for the other regioisomer, the hypothetical strong repulsion between the syn F (with its lone pairs) and the terminal nitrogen (with its lone pairs) which would be present in the transition state for formation of **13** could well be the rationale for preferred anti addition for this regioisomer.

Likewise, in the nitrileoxide cycloadditions, the stronger regioselectivity observed for the mesityl system, while being totally inconsistent with a steric rationale, can be understood in terms of the expected greater negative charge on the terminal oxygen for the mesitylnitrileoxide, hence the greater electrostatic repulsion for the fluorine end of the allene. The clear lack of *any* syn stereoselectivity in the nitrile oxide cycloadditions of **MFA** is certainly puzzling, particularly with respect to the **21/22** ratio. However, nitrileoxides, unlike nitrones, are *linear* molecules. Thus the substituent, in our cases phenyl and mesityl substituents, will be pointed right in the face of the fluorine substituent in the case of syn addition. It could therefore be that the aromatic π electrons act as a repulsive element in these syn transition states, which could in such a delicate balance of activation energies lead to the observed anti preference.

There is still another factor, one which presumably falls into the catagory of a "secondary orbital effect", which needs to be considered. This effect has been referred to by Cieplak[19], le Noble[20] and others[21] as the "hyperconjugation factor". Simply stated this factor predicts that "both nucleophiles and electrophiles [should]

approach trigonal carbon from the direction anti parallel to the electrorichest [allylic] single bond."[22] This prediction was predicated upon the principle that an anti periplanar σ bond should be able to delocalize into the newly developing σ* orbital (created in our case upon bond formation at C_2 of the allene).

le Noble, moreover, found that Diels-Alder reactions adhered to this prediction,[20] which when applied to cycloadditions of **MFA** would certainly predict *syn* π-facial selectivity since an antiparallel C-H σ bond should definitely be better hyperconjugating than a C-F σ bond.

Thus it appears that the syn π-facial diastereoselectivity which is observed in our 1,3-dipolar cycloadditions to **MFA** is at the first level, at least, consistent with Cieplak's and le Noble's hyperconjugation hypothesis. However, our observed switches from syn to anti preference which we have seen in the diazoalkane and nitrileoxide cycloadditions would not appear to be as easily reconciled by the hyperconjugation hypothesis as by the electrostatic interaction arguments.

Lastly, the results may be related to the observation by Gandolfi and DeMicheli of preferential syn addition of 1,3-dipoles to *cis*-3,4-dichloro- and *cis*-3,4-diacetoxycyclobutene.[23-25] In evaluating these results, calculations on *cis*-3,4-difluorocyclobutene by Caramella and Houk suggested that pyramidalization of the alkene carbons by the allylic fluorine substituents could influence the molecule's π-facial selectivity.[25] Indeed they suggested that the energetic effects of such interactions would be accentuated as the dipolarophile pyramidalizes to attain the transition state geometry. Interestingly, in their ab initio calculations Dixon and Smart found the carbon skeleton of fluoroallene to be slightly bent.[13]

Conclusions.

It should be clear from the above discussion that *no* definitive answer may be given at this time as to the cause of the regiochemical and stereochemical results which have been presented in this and previous papers relating to the cycloadditions of **DFA** and **MFA**. There are numerous factors which have the potential to provide effective rationales for the results.

Certainly, steric effects can play a role, such as in affecting the ratio of regioisomers in the cycloadditions of diazo compounds to these allenes, but they do not seem to play a determining role in the stereochemistry of **MFA**'s cycloadditions, or on the regiochemistry of **DFA**'s cycloadditions with nitrones or nitrileoxides.

While molecular orbital interactions are clearly dominant in determining the relative reactivity of the C_2-C_3 versus the C_1-C_2 π bonds of the allenes, it is very dubious whether such interactions play a role in the determination of the regiochemistry of cycloaddition with respect to the 1,3-dipoles; nor do they seem to be effective in explaining the stereochemistry of cycloadditions to **MFA**.

Electrostatic interactions seem to have considerable potential as a rationale for both the regiochemical and stereochemical results. However, the theory of such interactions, particularly with respect to 1,3-dipolar cycloadditions, is not adequately developed for one to reach any firm conclusions at this time. Other factors which will need to be considered in any analysis of these and related results are the "hyperconjugative" of Cieplak and le Noble, and the alkene pyramidalization effect proposed by Houk. Indeed, there may well be other factors not yet recognized which may end up being important, and in all likelihood the answer will end up involving a combination of a number of different factors.

The main thrust of *this* paper is experimental. The results which have been presented on the regio- and stereochemical outcome of 1,3-dipolar cycloadditions of difluoroallene and fluoroallene will need to be considered in any future theoretical rationale which is presented to explain the effect of substituents on this broad class of reactions.

Indeed, we believe that this work and our earlier published work demonstrates clearly that appropriately substituted allenes, with their perfectly aligned allylic bonds constitute ideal substrates for use in testing the theories of π-facial selectivity. We continue to pursue such investigations.

Acknowledgement. Helpful discussions with K. N. Houk, and the constructive comments of a referee are acknowledged. Support of this research in part by the National Science Foundation is gratefully acknowledged.

EXPERIMENTAL SECTION

All NMR spectra were recorded either on a Nicolet or Varian VXR instrument at 300 MHz for proton and 282 MHz for fluorine in $CDCl_3$ solution unless stated otherwise. Proton chemical shifts are reported in ppm downfield of TMS. Fluorine chemical shifts are reported in ppm upfield of $CFCl_3$.

(Z)-4-(Fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole 11a, (E)-4-(Fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole 12a, (Z)-5-(Fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole 13a, and (E)-5-(Fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole 14a. A solution of 2-diazopropane[26] (2.30 mmol) in anhydrous diethyl ether (15.0 mL) was prepared from acetone hydrazone and was pipetted into a small, dry, glass ampoule. The solution was chilled and degassed and then fluoroallene (0.14 g, 2.41 mmol) was condensed into the vessel which was sealed under vacuum. The tube was shaken well and set aside in the dark at room temperature. After about 45 min, the color of the diazo compound had disappeared. The tube was chilled, opened and the solvent removed by carefully blowing dry nitrogen over the reaction mixture. The product, a pale yellow liquid (0.27 g, 92%) was unstable unless stored in solution at dry ice temperature and consisted of four inseparable pyrazolines which were identified as (Z)-4-(fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole **11a** (37.8% of product by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 6.81 (dt, 1H, J_{HF} = 85.2 and J_{HH} = 2.3 Hz), 5.13 (dd, 2H, J_{HF} = 3.3 and J_{HH} = 2.3 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -131.4 (dt, J_{HF} = 85.2 and 3.3 Hz); (E)-4-(fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole **12a**, (23.3% of mixture by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 6.79 (dt, 1H, J_{HF} = 84.4 and J_{HH} = 2.8 Hz), 5.20 (dd, 2H, J_{HF} = 3.1 and J_{HH} = 2.8 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -126.8 (dt, J_{HF} = 84.4 and 3.2 Hz); (Z)-5-fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole **13a**, (4.2% of product by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 7.11 (dt, 1H, J_{HF} = 78 and J_{HH} = 2.2 Hz), 2.18 (dd, 2H, J_{HF} = 3.6 and J_{HH} = 2.3 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -131.6 (dt, J_{HF} = 78.0 and 3.5 Hz); (E)-5-(fluoromethylene)-4,5-dihydro-3,3-dimethyl-3H-pyrazole **14a**, (34.7% of product by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 8.11 (dt, 1H, J_{HF} = 78.0 and J_{HH} = 2.8 Hz), 2.28 (dd, 2H, J_{HF} = 3.6 and J_{HH} = 2.7 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -135.7 (dt, J_{HF} = 78.0 and 3.8 Hz); Mass Spectrum (mixture) gave exact mass (M^+-28) = 100.0692 ± 0.0009 (±9.0 ppm). Calculated mass for C_6H_9F is 100.0688, dev. + 0.0004 (+4.0 ppm).

(Z)-5'-(Fluoromethylene)-4',5'-dihydrospiro[9H-fluorene-9,3'-[3H] pyrazole] 13b, (E)-5'-(Fluoromethylene)-4',5'-dihydrospiro[9H-fluorene-9,3'-[3H]pyrazole] 14b, (Z)-2-(Fluoromethylene)spiro[cyclopropane-1,9'-[9H]-fluorene] 15b, (E)-2-(Fluoromethylene)spiro[cyclopropane-1,9'-[9H]-fluorene] 16b. To a small, dry glass ampoule was added freshly prepared 9-diazofluorene (0.52 g, 2.71 mmol) and anhydrous diethyl ether (10.0 mL). The tube contents were chilled and degassed on the vacuum line. Fluorallene (0.18 g, 3.10 mmol) was condensed into the tube which was then sealed under vacuum. The tube was set aside in the dark at room temperature and shaken occasionally. After about 48 hrs, the reaction mixture had turned yellow. The tube was chilled, opened and the solvent removed by carefully blowing dry nitrogen over the solution. The product, a viscous amber oil (0.69 g, 98%), was unstable unless stored in solution at low temperature and could not be separated into its four individual components. These were identified as (z)-5'-(fluoromethylene)-4',5'-dihydrospiro[9H-fluorene-9-3'-[3H]-pyrazole] **13b**, (8.8% of mixture by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 7.12-7.87 (m, 8H), 2.93 (t, 2H, J = 2.8 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -128.5 (dt, J_{HF} = 77.1 and 3.4 Hz); (E)-5'-(fluoromethylene)-4',5'-dihydrospiro[9H-fluorene-9,3'-[3H]pyrazole] **14b**, (59.3% of mixture by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 8.34 (dt, 1H, J_{HF} = 77.0 and J_{HH} = 2.7 Hz), 7.12-7.87 (m, 8H), 3.05 (t, 2H, J = 3.2 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -131.9 (dt, J_{HF} = 77.1 and 3.7 Hz); (Z)-2-(fluoromethylene)spiro[cyclopropane-1,9'-[9H]-fluorene] **15b**, (11.2% of mixture by NMR), ^{1}H NMR (mixture,

acetone-d_6) δ 7.12-7.87 (m, 8H), 2.47 (m, 2H); ^{19}F NMR (mixture, acetone-d_6) ϕ -125.4 (dt, J_{HF} = 88.4 and 5.9 Hz); (E)-2-(fluoromethylene)spiro[cyclopropane-1,9'-[9H]-fluorene] **16b**, (20.6% of mixture by NMR), ^{1}H NMR (mixture, acetone-d_6) δ 7.12-7.87 (m, 8H); 2.47 (m, 2H); ^{19}F NMR (mixture, acetone-d_6) ϕ -129.2 (dt, J_{HF} = 88.7 and 5.5 Hz); Mass Spectrum (mixture) gave exact mass (M^+-28) = 222.0854 ± 0.0018 (± 8.1 ppm). Calculated mass for $C_{16}H_{11}F$ is 222.0844, dev. + 0.0010 (+4.5 ppm).

(Z)-5-(Fluoromethylene)-4,5-dihydro-3,3-diphenyl-3H-pyrazole 13c, (E)-5-(Fluoromethylene)-4,5-dihydro-3,3-diphenyl-3H-pyrazole 14c, (Z)-1,1-Diphenyl-2-(fluoromethylene)cyclopropane 15c, and (E)-1,1-Diphenyl-2-(fluoromethylene)-cyclopropane 16c. To a small, dry, glass ampoule was added freshly recrystallized diphenyldiazomethane (0.20 g, 1.05 mmol) and anhydrous diethyl ether (3.0 mL). After chilling and degassing the solution, fluoroallene (0.10 g, 1.72 mmol) was condensed into the tube which was sealed under vacuum. The tube was set aside in the dark at room temperature and periodically shaken. After a period of 2-3 weeks, the contents of the tube had turned amber. The tube was chilled and opened and the solvent removed by carefully blowing dry nitrogen over the solution. The product, a viscous amber oil (0.25 g, 94%), was unstable unless stored in solution at low temperature. Separation of the mixture into individual components was not possible. The products were identified as (Z)-5-(fluoromethylene)-4,5-dihydro-3,3-diphenyl-3H-pyrazole **13c**, (8.9% of mixture by NMR), ^{1}H NMR (mixture, $CDCl_3$) δ 7.22-7.34 (m, 8H), 6.91 (dt, 1H, J_{HF} = 76.7 and J_{HH} = 2.3 Hz), 2.97 (dd, 2H, J_{HF} = 3.5 and J_{HH} = 2.1 Hz); ^{19}F NMR (mixture, $CDCl_3$) ϕ -127.6 (dt, J_{HF} = 76.7 and 3.3 Hz); (E)-5-(fluoromethylene)-4,5-dihydro-3,3-diphenyl-3H-pyrazole **14c**, (81.5% of mixture by NMR), ^{1}H NMR (mixture, $CDCl_3$) δ 8.02 (dt, 1H, J_{HF} = 76.9 and J_{HH} = 2.7 Hz), 7.22-7.34 (m, 8H), 3.13 (dd, 2H, J_{HF} = 3.7 and J_{HH} = 2.75 Hz); ^{19}F NMR (mixture, $CDCl_3$) ϕ -131.6 (dt, J_{HF} = 76.9 and 3.8 Hz); (Z)-1,1-diphenyl-2-(fluoromethylene)cyclopropane **15c**, (2.7% of mixture by NMR), ^{1}H NMR (mixture, $CDCl_3$) δ 7.22-7.34 (m, 8H), 2.02 (dd, 2H, J_{HF} = 4.7 and J_{HH} = 2.0 Hz); ^{19}F NMR (mixture, $CDCl_3$) ϕ -127.3 (dt, J_{HF} = 91 and 5.1 Hz); (E)-1,1-diphenyl-2-(fluoromethylene)cyclopropane **16c**, (6.9% of mixture by NMR), ^{1}H NMR (mixture, $CDCl_3$) δ 7.22-7.34 (m, 8H), 2.04 (dd, 2H, J_{HF} = 5.0 and J_{HH} = 2.6 Hz); ^{19}F NMR (mixture, $CDCl_3$) ϕ -131.7 (dt, J_{HF} = 89.6 and 5.0 Hz); Mass Spectrum (mixture) gave exact mass (M^+-28) = 224.1014 ± 0.0041 (± 18.7 ppm). Calculated mass for $C_{16}H_{13}F$ is 224.1001, dev. +0.0013 (+5.8 ppm).

(Z)-4-(Fluoromethylene)-4,5-dihydro-3-phenylisoxazole 21a, (E)-4-(Fluoromethylene)-4,5-dihydro-3-phenylisoxazole 22a, (Z)-5-(Fluoromethylene)-4,5-dihydro-3-phenylisoxazole 23a, and (E)-5-(Fluoromethylene)-4,5-dihydro-3-phenylisoxazole 24a. A dried ($CaCl_2$) solution of benzonitrile N-oxide in CCl_4 (15.0 mL) was prepared from benzhydroxamoyl chloride (3.40 g, 21.9 mmol) and stored at -10°C. An aliquot of this reagent (0.50 mL, 0.73 mmol N-oxide) together with acetone-d_6 (50 µL), was pipetted into a dry Wimad PP507 NMR tube. After chilling, degassing, and adding NMR standards ($CFCl_3$, TMS), fluoroallene (0.05 g, 0.86 mmol) was condensed into the tube which was then sealed under vacuum. The tube was then left in the dark at -10°C for 10 hrs. After this time, a pale yellow-colored product had been formed. This product was very unstable and was analyzed immediately by NMR without working up. NMR yields of 85-92% were calculated. Four fluorine-containing adducts were produced in this reaction and were identified by their characteristic NMR spectra taken from the reaction mixture. The products were (Z)-4-(fluoromethylene)-4,5-dihydro-3-phenylisoxazole **21a**, (4.0% of mixture by NMR), ^{1}H NMR (mixture, CCl_4, acetone-d_6) δ 7.30-7.86 (m, 5H), 5.07 (dd, 2H, J_{HF} = 5.0 and J_{HH} = 2.8 Hz); the olefinic =CHF was buried in the aromatic region; ^{19}F NMR (mixture, CCl_4, acetone-d_6) ϕ -118.3 (br d, J_{HF} = 76.7 Hz); (E)-4-(fluoromethylene)-4,5-dihydro-3-phenylisoxazole **22a**, (35.8% of mixture by NMR), ^{1}H NMR (mixture, CCl_4, acetone-d_6) δ 7.30-7.86 (m, 5H), 5.18 (dd, 2H, J_{HF} = 5.8 and J_{HH} = 4.0 Hz); the olefinic =CHF was buried in the aromatic region; ^{19}F NMR (mixture, CCl_4, acetone-d_6) ϕ -123.0 (br d, J_{HF} = 79.5 Hz); (Z)-5-(fluoromethylene)-4,5-dihydro-3-phenylisoxazole **23a**, (16.7% of mixture by NMR) ^{1}H NMR (mixture, CCl_4, acetone-d_6) δ 7.30-7.86 (m, 5H), 4.07 (dd, 2H, J_{HF} = 5.0 and J_{HH} = 3.0 Hz); the olefinic =CHF was buried in the aromatic region; ^{19}F NMR (mixture, CCl_4, acetone-d_6) ϕ -162.1 (br d, J_{HF} = 75.4 Hz); (E)-5-(fluoromethylene)-4,5-dihydro-3-phenylisoxazole **24a**, (43.5% of mixture by NMR), ^{1}H NMR (mixture, CCl_4, acetone-d_6) δ 7.30 - 7.86 (m, 5H), 4.19 (dd, 2H, J_{HF} = 6.0 and J_{HH} = 3.5 Hz); the olefinic =CHF was buried in the aromatic region; ^{19}F NMR (mixture, CCl_4, acetone-d_6) ϕ -177.8 (br d, J_{HF} = 78.3 Hz); Mass Spectrum (mixture) gave exact mass M^+ = 177.0589 ± 0.0071 (± 40.2 ppm due to low intensity). Calculated for $C_{10}H_8NOF$ is 177.0589, dev. -0.0001 (-0.5 ppm).

(Z)-4-(Fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole 21b, (E)-4-(Fluoromethylene)-

4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole 22b, (Z)-5-(Fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole 23b, and (E)-5-(Fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)- isoxazole 24b. To a dry Wilmad PP507 NMR tube was added recrystallized 2,4,6-trimethylbenzonitrile N-oxide (0.084 g, 0.52 mmol) and $CDCl_3$ (500 μL). After chilling, degassing, and adding internal NMR standards, fluoroallene (0.08 g, 1.37 mmol) was condensed into the tube which was sealed under vacuum. The tube was then set aside in the dark for 24 hrs at -10°C. The product was unstable and was examined by NMR immediately without work-up. The NMR yield was 92-95%. The products were (Z)-4-(fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole **21b**, (4% of mixture by NMR) ^1H NMR (mixture, $CDCl_3$) δ 6.91 (s, 2H), 5.16 (2H), 2.30 (s, 3H), 2.19 (s, 6H); the olefinic =CHF could not be seen; ^{19}F NMR (mixture $CDCl_3$) ϕ -126.0 (dt, J_{HF} = 79.0 and 6.7 Hz); (E)-4-(fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole **22b**, (85% of mixture by NMR), ^1H NMR (mixture, $CDCl_3$) δ 6.91 (s, 2H), 6.57 (dt, 1H, J_{HF} = 79.3 and J_{HH} = 4.0 Hz), 5.24 (dd, 2H, J_{HF} = 5.9 and J_{HH} = 4.0 Hz), 2.30 (s, 3H), 2.19 (s, 6H); ^{19}F NMR (mixture, $CDCl_3$) ϕ -125.8 (dt, J_{HF} = 79.3 and 5.7 Hz); (Z)-5-fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole **23b**, (4% of mixture by NMR),^1H NMR (mixture, $CDCl_3$) δ 6.91 (s, 2H), 3.90(m, 2H), 2.30 (s, 3H), 2.19 (s, 6H); the olefinic =CHF was not seen; (E)-5-(fluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole **24b**, (7% of mixture by NMR), ^1H NMR (mixture, $CDCl_3$) δ 6.91 (s, 2H), 4.03 (m, 2H), 2.30 (s, 3H), 2.19 (s, 6H); the olefinic =CHF was not seen; Mass Spectrum (mixture) gave exact mass M^+ = 219.1064 ± 0.0012 (±5.5 ppm). Calculated mass for $C_{13}H_{14}NOF$ is 219.1059, dev. + 0.0005 (+ 2.3 ppm).

(E)-2-(1,1-Dimethylethyl)-4-(fluoromethylene)isoxazolidine 9, and (Z)-2-(1,1-Dimethylethyl)-4-(fluoromethylene)isoxazolidine 10. To a small glass ampoule was added a freshly prepared solution of N-t-butylnitrone[14] (4.08 mmol) in CCl_4 (3.0 mL). The solution was chilled and degassed. Fluoroallene (0.24 g, 4.14 mmol) was then condensed into the tube which was sealed under vacuum. The tube was set aside in the dark at room temperature for 5 days with occasional shaking after which time the tube contents had become yellow. The tube was chilled, opened, and the solvent removed by carefully blowing dry nitrogen over the solution. A yellow oil (0.54 g, 83%) remained. The product contained two fluorine-containing adducts in the ratio of 78.2 : 21.8 (**9**:**10**) by ^{19}F NMR. Separation was achieved by flash column chromatography using a 2-in. column with sintered glass filter, silica gel and n-pentane/diethyl ether (95/5) eluant. As the products did not fluoresce, TLC plates were developed with iodine. Eluting first was the minor product, a pale yellow oil (0.08 g, 12%) identified as (Z)-2-(1,1-dimethylethyl)-4-(fluoromethylene)isoxazolidine **10**, ^1H NMR (100 MHz) δ 6.56 (dm, J_{HF} = 82.5 Hz, 1H), 4.48 (br s, 2H), 3.46 (m, 2H, non-first-order AB pattern), 1.18 (s, 9H); ^{19}F NMR (188 MHz) ϕ -133.5 (d, J_{HF} = 82.5 Hz); Mass Spectrum gave exact mass M^+ = 159.1047 ± 0.0018 (± 11.3 ppm). Calculated mass for $C_8H_{14}NOF$ is 159.1059, dev. - 0.0012 (-7.5 ppm). Eluting second was the major product, a pale yellow oil (0.32 g, 49%), identified as (E)-2-(1,1-dimethylethyl)-4-(fluoromethylene)isoxazolidine **9**, ^1H NMR (200 MHz) δ 6.61 (dm, 1H, J_{HF} = 82.7 Hz), 4.32 (s, 2H), 3.61 (br s, 2H), 1.13 (s, 9H); ^{13}C NMR (25 MHz) δ 25.0 (s), 48.0 (s), 57.2 (s), 65.4 (d, J_{CF} = 7.3 Hz), 123.5 (d, J_{CF} = 8.6 Hz), 139.6 (d, J_{CF} = 251.5 Hz); ^{19}F NMR (188 MHz) ϕ -133.4 (d, J_{HF} = 82.7 Hz); Mass Spectrum gave exact mass M^+ = 159.1050 ± 0.0015 (± 9.4 ppm). Calculated mass for $C_8H_{14}NOF$ is 159.1059, dev. - 0.0009 (-5.7 ppm).

(Z)-5-(Fluoromethylene)-4,5-dihydro-3,3-dideuterio-3H-pyrazole 11, (E)-5-(Fluoromethylene)-4,5-dihydro-3,3-dideuterio-3H-pyrazole 12. Diazomethane-d_2[9] was prepared in ether under N_2 with due precautions. It was allowed towarm to 25°C from liq. N_2 temp. in the presence of fluoroallene for 55 min. Afterward, the ether was removed by careful vacuum transfer to give a 54% isolated yield of a white solid which rapidly melted at 25°C. The product was quickly placed in an nmr tube with cold $CDCl_3$, and the tube sealed under vacuum and stored over dry ice. The product ratio (**11**/**12**) was determined to be 88:12 by nmr, and the isotopic purity of the products was shown to be >98%. A repeat of the same experiment led to identical results.

4-(Difluoromethylene)-4,5-dihydro-3-phenylisoxazole 18a and 5-(Difluoromethylene)-4,5-dihydro-3-phenylisoxazole 19a. A dried ($CaCl_2$) solution of benzonitrile N-oxide in CCl_4 (15.0 mL) was prepared from benzhydroxamoyl chloride (2.05 g, 13.2 mmol). An aliquot of this reagent (5.0 mL, 4.40 mmol) was pipetted into a small, dry glass ampoule, chilled and degassed on the vacuum line. Difluoroallene (0.41 g, 5.52 mmol) was then condensed into the tube, which was sealed under vacuum. The tube was then allowed to stand in the dark at room temperature for 1 hr. It was then chilled and opened and the solvent removed by careful rotary evaporation. The product, a pale yellow oil (0.68 g, 73% based on starting benzhydroxamoyl chloride) was examined by ^{19}F

NMR and shown to contain three components. The product was separated by flash column chromatography using a 3.5-in. column with a sintered glass filter, silica gel and n-pentane eluant. Eluting first was 4-(difluoromethylene)-4,5-dihydro-3-phenylisoxazole **18a** (0.29 g, 34%) an unstable pale yellow oil, ^{1}H NMR (acetone-d_6) δ 7.44-7.83 (m, 5H), 5.22 (dd, 2H, J_{HF} = 6.0 and 5.6 Hz); ^{19}F NMR (acetone-d_6) ϕ -76.6 (dtt, 1F, J_{FF} = 31.6, J_{HH} = 6.1 and 2.7 Hz), -80.1 (dt, 1F, J_{FF} = 31.6 and J_{HF} = 5.6 Hz); the product contained a major impurity which was apparent in the ^{19}F NMR (ϕ -79.4, d, J_{HF} = 7.1 Hz, 28% assuming two fluorines); ^{13}C NMR δ 71.4 (s), 95.0 (t). 123.2 (s), 127.8 (s), 129.2 (s), 130.9 (s), 148.5 (t, J_{CF} = 289.5 Hz); IR (CCl_4) 3072, 2935, 2878, 1754 (s), 1592, 1377, 1280, 1119, 890, 694 cm^{-1}; Mass Spectrum gave exact mass M^+= 195.0514 ± 0.0013 (± 7.1 ppm). Calculated for $C_{10}H_7NOF_2$ = 195.0495, dev. +0.0018 (+9.4 ppm). Eluting second, with a much longer retention time, was 5-(difluoromethylene)-2,5-dihydro-3-phenylisoxazole **20** (0.24 g, 28%), a yellow crystalline solid, mp 155-157°C (dec.), ^{1}H NMR (acetone-d_6) δ 8.66 (br s, 1H), 7.96-8.00 (m, 2H), 7.69-7.75 (m, 1H), 7.59-7.65 (m, 2H), 5.81-5.84 (m, 1H); ^{19}F NMR ϕ -99.1 (dd, J_{FF} = 30.8 and J_{HF} = 2.2 Hz); ^{13}C NMR δ 95.1 (s), 111.9 (s), 128.3 (s), 129.2 (s), 130.1 (s), 134.6 (s), 153.0 (t, J_{CF} = 275.7 Hz); IR (CCl_4) 3280 (br), 1604, 1591, 1563, 1495, 1267, 1182, 1077, 778 cm^{-1}; Mass Spectrum gave exact mass M^+ = 195.0493 ± 0.0010 (5.6 ppm). Calculated for $C_{10}H_7NOF_2$ = 195.0495, dev. = -0.0002 (-1.3 ppm). The third component could not be isolated pure as it rapidly tautomerized to **20** on standing in solution, or on passing through silica gel. This was identified as 5-(difluoromethylene)-4,5-dihydro-3-phenylisoxazole **19a**, ^{1}H NMR (mixture, acetone-d_6) δ 7.40-7.73 (m, 5H), 4.20 (dd, 2H, J_{HF} = 6.3 and 5.5 Hz); ^{19}F NMR (mixture, acetone-d_6) ϕ -102.7 (dt, 1F, J_{FF} = 100.7 and J_{HF} = 5.4 Hz), -118.8 (dt, 1F, J_{FF} = 100.7 and J_{HF} = 6.3 Hz).

4-(Difluoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole 18b. To a small, dry glass ampoule was added 2,4,6-trimethylbenzonitrile N-oxide (0.60 g, 3.68 mmol) and anhydrous diethyl ether (15.0 mL). After chilling and degassing the solution, difluoroallene (0.37 g, 4.87 mmol) was condensed into the tube which was then sealed under vacuum. The tube was set aside in the dark at room temperature, occasionally shaking it. After 12 hrs, the tube was chilled and opened and the solvent carefully removed on the rotary evaporator. A colorless oil (0.82 g, 94%) was recovered and purified by flash column chromatography (silica gel/n-pentane). The pure product, a colorless oil (0.68 g, 78%) was identified as 4-(difuoromethylene)-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazole **18b**, ^{1}H NMR δ 6.90 (s, 2H), 5.24 (t, J = 6.1 Hz, 2H), 2.29 (s, 3H), 2.22 (s, 6H); ^{13}C NMR δ 18.5 (s), 21.0 (s), 69.4 (s), 125.5 (s), 128.7 (s), 136.6 (s), 139.6 (s), 139.4 (s), 149.5 (t, J_{CF} = 290.0 Hz); ^{19}F NMR ϕ -77.5 (dt, J_{FF} = 26.7 and J_{HF} = 5.5 Hz, 1F), -79.2 (dt, J_{FF} = 26.7 and J_{HF} = 6.3 Hz, 1F); IR (film) 3100, 2912, 1827, 1750 (s), 1612, 1457, 1357, 1273, 1146, 1109, 918 cm^{-1}; Mass Spectrum gave exact mass M^+ = 237.0976 ± 0.0022 (±9.6 ppm). Calculated mass for $C_{13}H_{13}NOF_2$ is 237.0965, dev. + 0.0010 (+ 4.5 ppm).

4-(Difluoromethylene)-2-(1,1-dimethylethyl)isoxazolidine 8. To a small, dry glass ampoule was added a freshly prepared solution of N-t-butylnitrone (4.08 mmol) in CCl_4 (3.0 mL). The solution was chilled and degassed and then difluoroallene (0.32 g, 4.21 mmol) was condensed in. The tube was sealed under vacuum and stored in the dark at room temperature for 16 hrs. After this time, the tube was chilled, opened, and the solvent carefully removed by rotary evaporation. The product, a pale yellow oil (0.62 g, 86%), was purified by flash column chromatography using silica gel and n-pentane, giving 4-(difluoromethylene)-2-(1,1-dimethylethyl)isoxazolidine **8** (0.59 g, 82%), ^{1}H NMR (200 MHz) δ 4.38 (br s, 2H), 3.50 (br s, 2H), 1.16 (s, 9H); ^{13}C NMR (25 MHz) δ 24.0 (s), 46.7 (s), 57.0 (s), 64.3 (s), 90.8 (t, J_{CF} = 23.2 Hz), 148.0 (t, J_{CF} = 282.0 Hz); ^{19}F NMR (188 MHz) ϕ -90.6 (non-first-order AB pattern); IR (film) 2974, 2938, 2910, 2862, 1794 (s), 1363, 1270, 1188, 1089, 1034, 810 cm^{-1}; Mass Spectrum gave exact mass M^+ = 177.0968 ± 0.0011 (± 6.4 ppm). Calculated mass for $C_8H_{13}NOF_2$ is 177.0965, dev. + 0.0003 (+1.7 ppm).

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17. For more detail, see also: "On the Use of Isovalued Surfaces to Determine Molecule Shape and Reaction Pathways", G. D. Purvis III, CAChe Technical Report #1, Tektronix, Inc., P. O. Box 500 M. S. 13-400, Beaverton, OR 97077.
18. A referee has suggested that one can explain the regiochemical variation of the diazoalkane cycloadditions on the basis of simple orbital charge control, since the negative charges at the carbon versus the N termini of the diazoalkanes seem to vary in such a way[16] that correlation is possible, assuming that the most "negative" terminus of the diazoalkane would attack the CH_2=C= allene site of lowest charge (i. e., C_2).[13] Indeed, perhaps looking at specific net partial charges of the bonding atoms *is* the best way to look at the electrostatic interactions between the reactants.
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