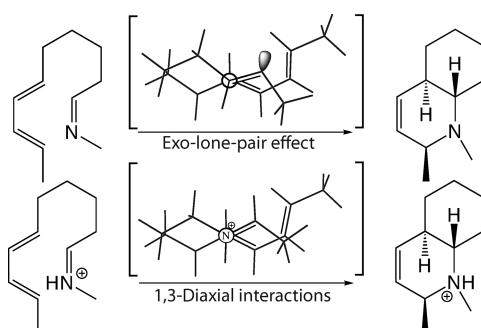# Intramolecular Hetero-Diels−Alder Reactions of Imine and Iminium Dienophiles: Quantum Mechanical Exploration of Mechanisms and Stereoselectivities

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A series of intramolecular hetero-Diels−Alder reactions of iminium and imine dienophiles has been explored with density functional theory using the B3LYP functional and 6-31+G* basis set. Aqueous solvation energies were calculated with the CPCM method. DFT predicts that these reactions are concerted but involve highly asynchronous transition states. Stereochemical preferences of imine cycloaddition transition states arise from electron repulsion of the nitrogen lone pair with electron density from the butadiene moiety. Protonation of the nitrogen leads to a highly asynchronous transition state. The iminium dienophiles are predicted to have a 17 kcal/mol lower barrier than the corresponding imines, even in aqueous solution.

Introduction

Aza-Diels−Alder reactions of imine derivatives with substituted 1,3-dienes have been used extensively in the stereoselective synthesis of alkaloids.[1,2] Since the first intramolecular hetero-Diels−Alder reaction of iminium dienophiles was reported by Grieco et al. in 1985,[3] much attention has been focused on the generality, mechanism, and application of these reactions in synthesis. Dienes and aldiminium ions (Scheme 1), easily generated in situ under Mannich-like conditions, give Diels−Alder adducts in reasonable yields.[4]

There are several possible mechanisms for these reactions (Scheme 2): (1) a concerted [4 + 2] Diels−Alder reaction proceeding through a transition state similar to TS_A; (2) a stepwise mechanism proceeding through a diradical intermediate such as TS_B; and (3) a stepwise mechanism involving an allyl cation intermediate such as TS_C. The two stepwise pathways are appealing. The diradical path involves an allyl radical intermediate, the stability of which may be reflected in a low-

(1) (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press: New York, 1987; pp 49−70. (b) Weinreb, S. M. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 5, pp 401−449.

(2) (a) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263. (b) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707. (c) Heathcock, C. H.; Hansen, M. M.; Ruggeri, R. B.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2544. (d) Bailey, P. D.; Londesbrough, D. J.; Hancox, T. C.; Heffernan, J. D.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1994**, 2543. (e) Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 14323. (f) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633. (g) Cuerva, J. M.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Commun.* **1999**, 1721. (h) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (i) Sabitha, G.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2001**, *10*, 1979. (j) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941. (k) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (l) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913. (m) Mayekar, N. V.; Nayak, S. K.; Chattopadhyay, S. *Synth. Commun.* **2004**, *34*, 3111.

(3) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

(4) (a) Stella, L.; Abraham, H.; Feneu-Dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603. (b) Hedberg, C.; Pinho, P.; Roth, P.; Anderson, P. G. *J. Org, Chem*, **2000**, *65*, 2810.

SCHEME 1. Intramolecular Diels−Alder Reactions of Aldiminium Salts[3]
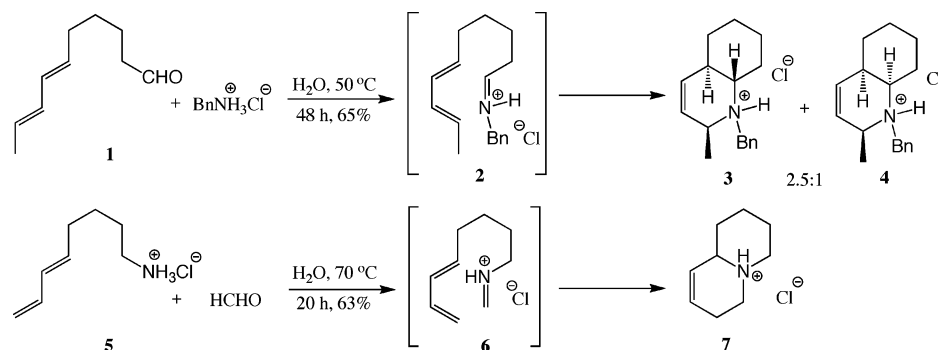
SCHEME 2. Possible Mechanisms for the Intramolecular Hetero-Diels−Alder Reaction of Iminium Dienophiles
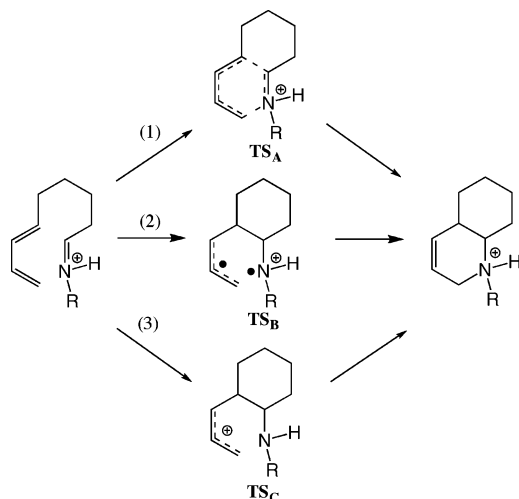
energy intermediate. Similarly, the allyl cation intermediate should also be relatively stable.

Bartlett and co-workers reported use of intramolecular aza-Diels−Alder reactions for combinatorial chemical applications using an "aldehyde−bridge−alkene" motif as the key component.[5,6] Various substrates, including substituted salicylaldehydes, glyoxylic esters and amides, and N-acyl-α-aminoaldehydes, were reacted with a series of anilines to generate a chemical library comprised of structurally diverse compounds built around a quinoline core (Scheme 3).

In 2000, MacMillan defined the general concept of the activation of α,β-unsaturated carbonyl compounds with an external secondary amine catalyst.[7] As illustrated in Scheme 4a, an α,β-unsaturated aldehyde can be activated by the reversible formation of an iminium ion with an external amine catalyst. MacMillan et al. investigated intramolecular Diels−Alder reactions of several trienals and applied this methodology to a short enantioselective synthesis of solanapyrone D.[8] As depicted in Scheme 4b, treatment of **17** with 20 mol % of catalyst **18** gave the decalin **19** in 17% yield with 90% ee. The aldehyde **19** was converted to solanapyrone D in five additional steps.

Kerwin and Danishefsky reported several cyclocondensations of imines with electron-rich dienes.[9] Ojima and co-workers (Scheme 5a) studied reactions of ketene silyl acetals with imines catalyzed with titanium tetrachloride.[10] Both cyclic and acylic products were formed, and it was concluded that a common intermediate leads to both products. Midland and McLaughlin's work (Scheme 5b) with Brassard's diene[11] provided evidence for a concerted mechanism by isolating cyclic products as a single diastereoisomer.[12] More recent mechanistic studies by Whiting et al. (Scheme 5c) showed evidence of non-concertedness, and a stepwise addition−cyclization mechanism was proposed.[13]

A number of theoretical studies of hetero-Diels−Alder reactions have been reported.[14] The reaction of formaldimine and 1,3-butadiene was studied with ab initio molecular orbital calculations. At all calculated levels of theory (HF/3-21G*, HF/6-31G*, MP2/6-31G*, and B3LYP/6-31G*), asynchronous concerted exo and endo transition states (TSs) were characterized. Lower levels of theory produce more synchronous TSs.

The hetero-Diels−Alder reactions of a series of imines and butadiene show exo selectivity with respect to the lone pair on the nitrogen.[14f] Previous studies from our laboratory showed that this exo-lone-pair effect arises from repulsive n−π interactions. The exo-lone-pair conformation was calculated to be 4−6 kcal/mol lower in energy than the endo isomer, as shown in Figure 1. These studies showed that the stereochemical outcome

(5) (a) Spaller, M. R.; Thielemann, W. T.; Brennan, P. E.; Bartlett, P. A. *J. Comb. Chem.* **2002**, *4*, 516. (b) Muhuhi, J.; Spaller, M. R. *J. Org. Chem.* **2006**, *71*, 5515.

(6) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153.

(7) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575.

(8) Wilson, R. M.; Jen, W. S.; MacMillan, W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.

(9) Kerwin, J. F.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 3739.

(10) Brandstadter, S. M.; Okima, I.; Hirai, K. *Tetrahedron Lett.* **1987**, *28*, 613.

(11) Brassard, P.; Savard, J. *Tetrahedron Lett.* **1979**, *20*, 4911.

(12) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.* **1988**, *29*, 4653.

(13) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451.

(14) (a) Tietze, L. F.; Fennen, J.; Anders, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1371. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (c) Tran Huu Dau, M. E.; Flament, J.-P.; Lefour, J.-M.; Riche, C.; Grierson, D. S. *Tetrahedron Lett.* **1992**, *33*, 2343. (d) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992**, *57*, 6736. (e) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1499. (f) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330. (g) Jursic, B. S.; Zdravkovski, Z. *J. Org. Chem.* **1994**, *59*, 7732. (h) Tietze, L. F.; Fennen, J.; Geibler, H.; Schulz, G.; Anders, E. *Liebigs Ann.* **1995**, 1681. (i) Venturini, A.; Joglar, J.; Fustero, S.; Gonzalez, J. *J. Org. Chem.* **1997**, *62*, 3919. (j) Whiting, A.; Windsor, C. M. *Tetrahedron* **1998**, *54*, 6035. (k) Tietze, L. F.; Pfeiffer, T.; Schuffenhauer, A. *Eur. J. Org. Chem.* **1998**, 2733. (l) Park, Y. S.; Lee, B.-S.; Lee, I. *New J. Chem.* **1999**, *23*, 707. (m) Mayr, H.; Ofial, A. R.; Sauer, J.; Schmied, B. *Eur. J. Org. Chem.* **2000**, 2013. (n) Tantillo, D. J.; Houk, K. N; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938. (o) Vijaya, R.; Sastry, G. N. *J. Mol. Struct. (THEOCHEM)* **2002**, *618*, 201−208. (p) Su, M.-D. *Organometallics* **2004**, *23*, 2507.

SCHEME 3.   Combinatorial Applications of Intramolecular Hetero-Diels−Alder Reactions[5,6]
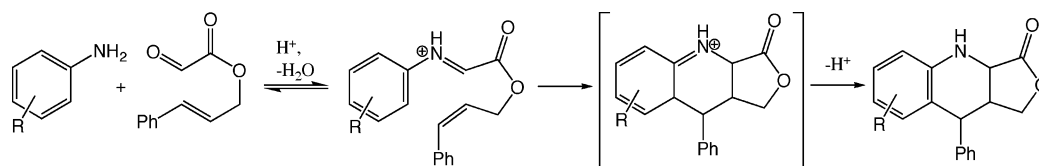
SCHEME 4.   (a) General Diels−Alder Activation with Secondary Amines and (b) Synthesis of Solanapyrone D with Iminium Catalysis
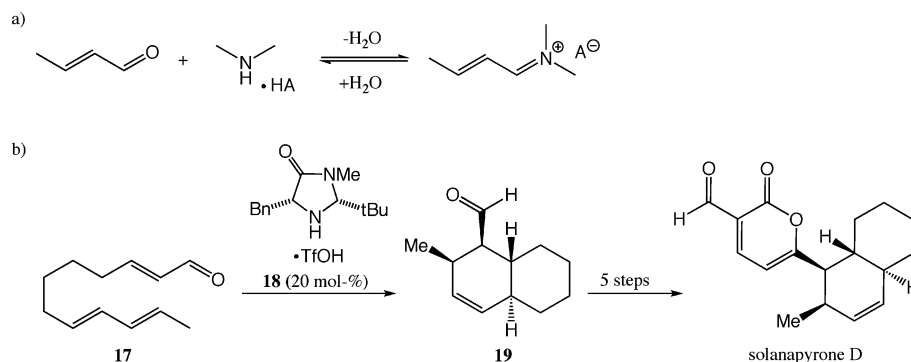

SCHEME 5.   Previous Work on Lewis Acid-Catalyzed Aza-Diels−Alder Reactions[10,12,13]
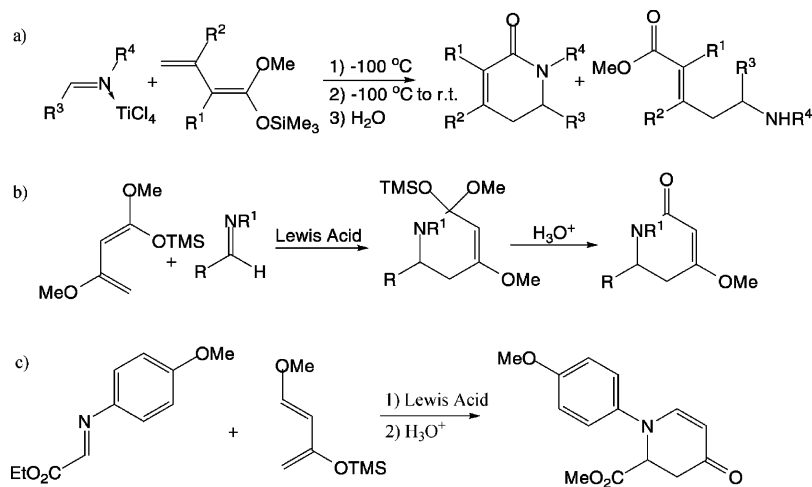
of bimolecular aza-Diels−Alder reactions of imines is greatly influenced by the lone-pair electrons on the nitrogen atom.[14f]

Theoretical and experimental studies of the bimolecular aza-Diels−Alder reaction of formaldiminium and 1,3-butadiene have given less conclusive results. HF/3-21G calculations support an asynchronous transition structure.[14e] Mayr and co-workers presented a joint experimental/theoretical study of the cycloadditions of iminium cations and several butadienes.[14m] Kinetic studies of the reaction of *N,N*-dimethylmethyleneammonium ion and cyclopentadiene showed evidence of a concerted mechanism because the s-*cis*-fused ring system prevented rotation about the σ bond. Calculations at the HF/6-31G level further supported these results, predicting that the highly asynchronous, concerted process is favored by 6.4 kcal/mol over the stepwise reaction.[14m]

Some acid-catalyzed aza-Diels−Alder reactions proceed via TSs that closely resemble intermediate allyl cations. Ab initio calculations by Domingo and co-workers showed that the reaction between cyclopentadiene and different formaldiminium cations occurs along a highly asynchronous concerted pathway; the reaction has polar character that typifies a nucleophilic attack

of the cyclopentadiene on the ylidene ammonium cation.[15] The reaction between cyclopentadiene and protonated pyridine-2-carboxaldehyde imine derivatives proceeds via a polar stepwise mechanism (Scheme 6).[16] The polar iminium dienophile is

SCHEME 6.   System Studied by Domingo and Co-workers[16]
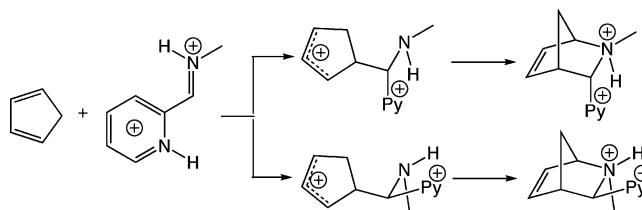
expected to be highly reactive, and the high electrophilicity of the carbon of the iminium ion could divert the reaction to a stepwise process.

(15) Domingo, L. R. *J. Org. Chem.* **2001**, *66*, 3211.
(16) Domingo, L. R.; Oliva, M.; Andrés, J. *J. Org. Chem.* **2001**, *66*, 6151.
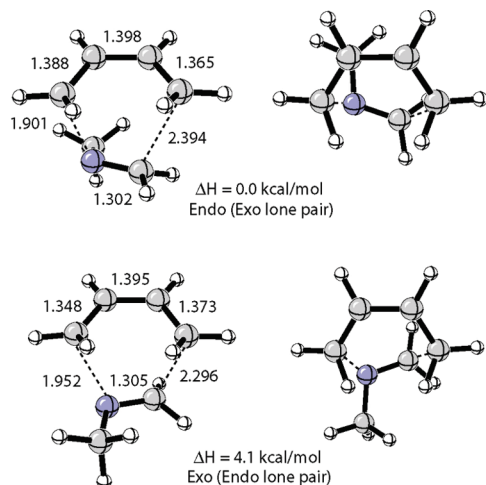
FIGURE 1. Energy difference between exo and endo lone-pair transition states at the HF/3-21G level of theory.[14f]

We have investigated the intramolecular hetero-Diels−Alder reactions of iminium and imine dienophiles. Computational methods that have been shown to be reliable for related rearrangements were employed.[17] These cycloadditions are found to proceed via asynchronous, concerted mechanisms. The reactions are predicted to proceed stereoselectively, with the iminium dienophiles favoring a *trans* cycloadduct, but imine dienophiles prefer a TS that has the lone pair of the nitrogen exo.

Computational Methods

Calculations were performed with the Gaussian 03[18] suite of programs. The potential energy surfaces (PES) were initially characterized at the HF/6-31+G* level of theory to locate all stationary points. All minima and transition structures were verified by vibrational frequency calculations. These stationary points were further refined via optimization at the B3LYP/6-31+G* level of theory. HF/6-31+G* energies can be found in the Supporting Information. Previous theoretical studies of cycloadditions have shown that DFT calculations using the B3LYP functional[19] are in reasonable agreement with experimental activation energies of hydrocarbon pericyclic processes and compare well with CASPT2 and CBS-QB3 predictions.[17] Diradicals and TSs leading to diradicals were treated using spin-unrestricted calculations; UB3LYP (guess= mix,always) optimizes structures identical with the closed-shell species.

Solvation free energies were computed with CPCM calculations: B3LYP/6-31+G* optimizations of stationary points using a self-consistent reaction field based on the Cosmo Polarizable Continuum Model (CPCM-SCRF)[20] in Gaussian 03. A dielectric constant of 78.39 was used to simulate aqueous environment. Calculations were performed using UAKS cavities which use the

(17) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445.

(18) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. See the Supporting Information for the full citation.

(19) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(20) (a) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799. (b) Andzelm, J.; Kölmel, C.; Klamt, A. *J. Chem. Phys.* **1995**, *103*, 9312. (c) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. (d) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669. (e) Takano, Y.; Houk, K. N. *J. Chem. Theory Comput.* **2005**, *1*, 70.

SCHEME 7. Reactions Studied Computationally
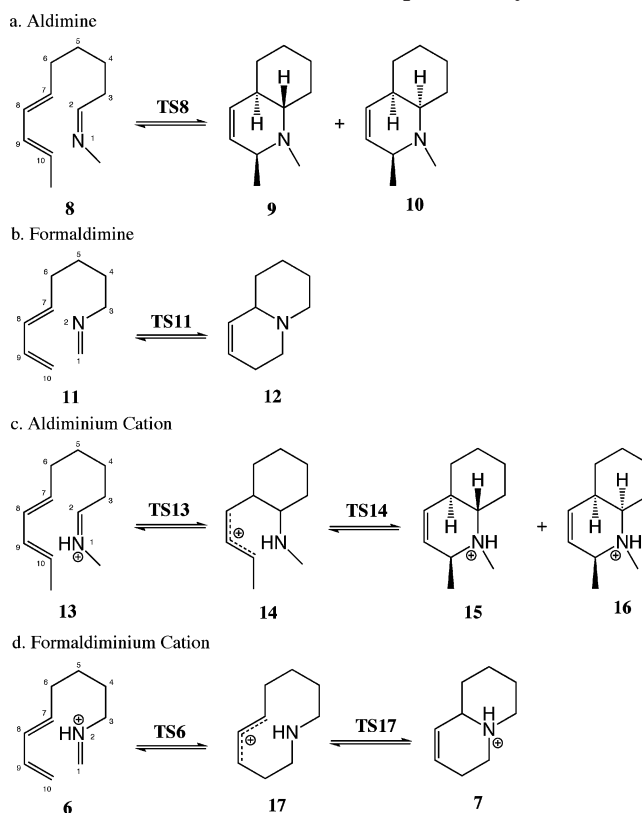
United Atom Topological Model (UATM) applied on radii optimized for the PBE0/6-31G* level of theory.[21]

Results and Discussion

The four intramolecular cycloadditions studied here are shown in Scheme 7. *N*-Methyl aldiminium cation **13** (Scheme 7) was substituted for *N*-benzyl aldiminium cation **2** (Scheme 1) to avoid conformational complications. The Z and E nomenclature refers to the stereochemistry of the aldiminium cation in the reactant. *Trans* and *cis* refer to the stereochemistry of the fused rings in the product.

Mechanism of Intramolecular Aza-Diels−Alder Reaction of Imine Dienophiles. Predicted activation energies, energies of reactions, and product ratios for the intramolecular aza-Diels−Alder reactions of imine dienophiles (**8** and **11**) are provided in Table 1. To establish the nature of the mechanism of these hetero-Diels−Alder reactions, the reactions of aldimine **8** and formaldimine **11** were studied in detail.

The DFT results for the reaction of aldimine **8-E** show that the intramolecular cycloaddition takes place along an asynchronous concerted pathway. Two TSs and two cycloadducts, *cis*- and *trans*-fused, have been found and characterized. DFT predicts ΔH_{rxn} values of −8.9 and −6.7 kcal/mol for formation of *trans* and *cis* products (**9** and **10**), respectively. The geometries of the corresponding transition states (**TS8-E-*trans*** and **TS8-E-*cis***) are presented in Figure 2. The concerted pathway leading to *trans* cycloadduct **9** is preferred, with $\Delta H^{\ddagger}$ = 36.2 kcal/mol. This *trans* pathway features an exo lone pair, and **TS8-E-*trans*** is fairly synchronous. This is in contrast to

(21) (a) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639. (b) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.

TABLE 1. Gas Phase ($\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$) and Aqueous Phase ($\Delta G^{\ddagger}_{solv}$) B3LYP/6-31+G* Gibbs Free Energies (kcal/mol) and *Trans*:*Cis* Product Ratios for the Intramolecular Hetero-Diels−Alder Reactions of Imine Dienophiles
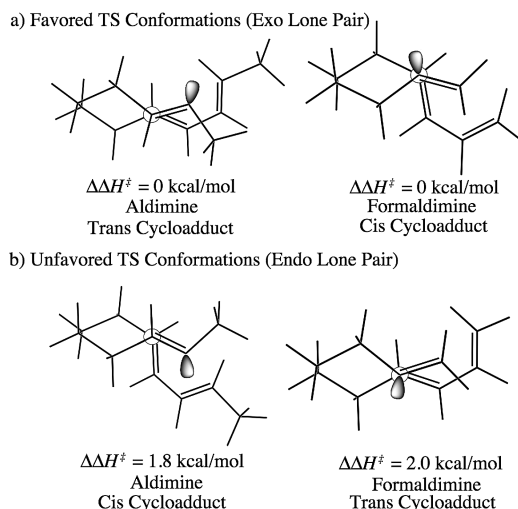
	trans			*cis*				*trans*:*cis*
reactant	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{solv}$)	ΔH_{rxn}	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{solv}$)	ΔH_{rxn}	$\Delta\Delta H^{\ddagger}$(*cis−trans*)	[gas (solv)]
8-E	36.2	42.5 (43.4)	−8.9	38.1	44.1 (44.7)	−6.7	1.8	15:1 (9:1)
8-Z	34.0	40.8 (42.6)	−13.0	33.2	40.2 (40.9)	−10.8	−0.8	1:3 (1:18)
11	31.7	37.1 (35.7)	−22.3	29.7	34.9 (34.7)	−17.6	−2.0	1:43 (1:5)

TS8-E-*cis*   **TS8-E-*trans***

TS8-Z-*cis*   **TS8-Z-*trans***
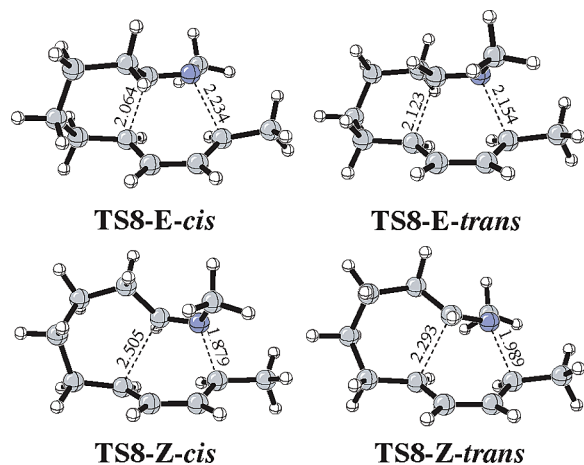
FIGURE 2. B3LYP/6-31+G* transition structures for the intramolecular hetero-Diels−Alder reaction of aldimine **8-E** and **8-Z**.

TS11-*cis*   **TS11-*trans***
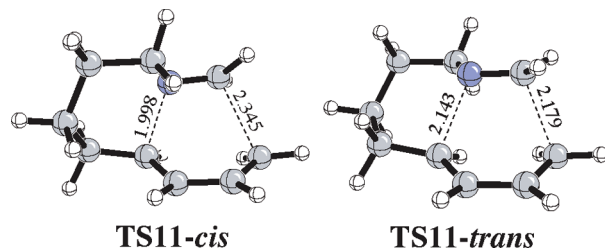
FIGURE 3. B3LYP/6-31+G* transition structures for the intramolecular hetero-Diels−Alder reaction of formaldimine **11**.

TS8-E-*cis*, in which the forming bonds differ by 0.17 Å. B3LYP-constrained minimizations along the reaction path linking the TS with the product were performed in order to locate any stable intermediates. However, no intermediate or second TS structure exists.

The reaction enthalpies of **8-Z** are −13.0 and −10.8 kcal/mol for the *trans* and *cis* cycloadducts, respectively. The geometries of **TS8-Z-*trans*** and **TS8-Z-*cis*** are presented in Figure 2. The TSs are both quite asynchronous. The *cis* transition structure, with an exo lone pair, is predicted to have the lower activation barrier, and no intermediate or stepwise TS could be located.

For imine **11**, reaction enthalpies of −17.6 and −22.3 kcal/mol are predicted for the formation of the *trans* and *cis* conformations of cycloadduct **12**, respectively. The geometries of **TS11-*cis*** and **TS11-*trans*** are presented in Figure 3. The energetically preferred endo transition structure **TS11-*cis***, with exo lone pair, is very asynchronous. The predicted enthalpy barrier for the concerted pathway is 29.7 kcal/mol, yielding the *cis* conformation of cycloadduct **12**. The barrier for cyclization to the *trans* isomer (endo lone pair) of the imine is approximately 2.0 kcal/mol higher in energy. The TS of the cycloaddition of **11** involves asynchronous bond formation. N1−C10 bond formation is favored due to the syn-clinal arrangement

a) Favored TS Conformations (Exo Lone Pair)

$\Delta\Delta H^{\ddagger} = 0$ kcal/mol
Aldimine
Trans Cycloadduct

$\Delta\Delta H^{\ddagger} = 0$ kcal/mol
Formaldimine
Cis Cycloadduct

b) Unfavored TS Conformations (Endo Lone Pair)

$\Delta\Delta H^{\ddagger} = 1.8$ kcal/mol
Aldimine
Cis Cycloadduct

$\Delta\Delta H^{\ddagger} = 2.0$ kcal/mol
Formaldimine
Trans Cycloadduct

FIGURE 4. Newman projections of imine transition structures to emphasize lone-pair locations.

TABLE 2. Dihedral Angles ($\phi_{C-N-C-C}$) at B3LYP/6-31+G* Optimized Geometries for the *Cis* and *Trans* Transition States for the Intramolecular Hetero-Diels−Alder Reactions of Imine Dienophiles

	$\phi_{C-N-C-C}$	
reactant	*trans* path	*cis* path
8-E	13.0	−18.6
8-Z	−34.3	32.6
11	−15.3	20.0

of the N1−C2 and the C7−C8 bonds. There is an obvious preference for the formation of *trans*-fused products, thermodynamically, but the transition state stabilities are dominated by the exo-lone-pair effect.[14f]

This exo-lone-pair effect[14f] arises from electrostatic interactions of the nitrogen lone pair with the diene π moiety with the disfavored endo lone-pair transition state. Reactions containing an imine show a 0.8−2.0 kcal/mol preference for the lone-pair electrons on the imine to be exo with respect to the butadiene moiety, as shown in Figure 4. The dihedral angles ($\phi_{C-N-C-C}$) of all TSs studied are given in Table 2. Dihedral angles for the energetically unfavorable TSs of the intramolecular aza-Diels−Alder of aldimine **8** are larger than the corresponding dihedral angles in the favorable TSs. The dienophile is skewed, minimizing the electrostatic interactions. The trend is reversed for formaldimines, and the energetically unfavorable TS now has a smaller dihedral angle. The forming C−N bond of **TS11-*cis*** is more advanced in the TS. The dihedral of the **TS11-*cis*** is larger because the dienophile adopts an equatorial position about the forming ring while still allowing orbital overlap necessary for a Diels−Alder reaction. Therefore, in situations where multiple conformations are possible, the most likely TS is expected to occur when gauche interactions are minimized and the lone-pair electrons are exo to the diene. This is a powerful

TABLE 3. Gas Phase ($\Delta H^{\ddagger}$, $\Delta G^{\ddagger}$) and Aqueous Phase ($\Delta G^{\ddagger}_{solv}$) B3LYP/6-31+G* Gibbs Free Energies (kcal/mol) and *Trans:Cis* Product Ratios for the Intramolecular Hetero−Diels−Alder Reactions of Iminium Dienophiles

| | *trans* | | | *cis* | | | | *trans:cis* |
reactant	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{solv}$)	ΔH_{rxn}	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_{solv}$)	ΔH_{rxn}	$\Delta\Delta H^{\ddagger}(cis-trans)$	[gas (solv)]
13-E	9.3	14.0 (26.0)	−15.1	10.1	15.2 (27.3)	−15.2	0.9	8:1 (9:1)
13-Z	8.5	13.7 (25.2)	−20.8	9.7	15.2 (26.4)	−16.0	1.2	12:1 (7:1)
6	3.1	8.1 (17.7)	−37.0	4.4	9.2 (17.6)	−33.9	1.3	6:1 (1:1)
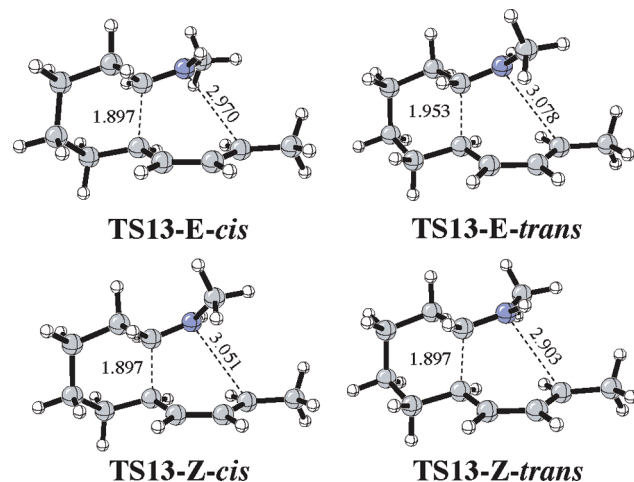
FIGURE 5. B3LYP/6-31+G* Transition structures for the intramolecular hetero−Diels−Alder reaction of aldiminium **13-E** and **13-Z**.
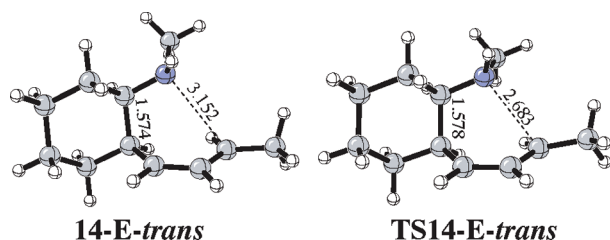
FIGURE 6. HF/6-31+G* ring-closing transition state **TS14-E-*trans***, and intermediate **14-E-*trans*** for the intramolecular hetero−Diels−Alder reaction of aldiminium **13-E**.

example of the exo-lone-pair effect and its application to intramolecular aza-Diels−Alder reactions.[14f]

Mechanism of Intramolecular Aza-Diels−Alder Reactions of Iminium Dienophiles. Predicted activation enthalpies and free energies for the intramolecular reactions of iminium dienophiles (**13** and **6**) are provided in Table 3. The reactions of aldiminium **13** and formaldiminium **6** were studied to establish the features of the mechanism of these hetero−Diels−Alder reactions.

DFT results for the reaction of aldiminium **13-E** provide evidence that this intramolecular cycloaddition takes place along a highly asynchronous concerted pathway. Two transition structures and two cycloadducts were characterized for the reaction of **13-E**. DFT predicts ΔH_{rxn} values of −15.1 and −15.2 kcal/mol for formation of the *trans*- and *cis*-fused cycloadducts (**15-*trans*** and **16-*cis***), respectively. The geometries of the corresponding transition states (**TS13-E-*cis*** and **TS13-E-*trans***) are presented in Figure 5. The concerted pathway leading to the *trans* cycloadduct **15-*trans*** is preferred with an activation enthalpy of 9.3 kcal/mol. B3LYP calculations agree with

experiment, predicting the stereochemical preference for formation of the *trans* cycloadduct.[22]

DFT calculations with solvent corrections predict Brønsted acid catalysis by a proton to increase the reaction rate by 4.5 × 10^{12}. In other words, intramolecular hetero-Diels−Alder reactions of iminium dienophiles at room temperature occur quickly, whereas imine dienophiles would react only within a few centuries.

The cycloaddition of **13-E** is associated with highly asynchronous bond formation that is strongly influenced by the more electrophilic carbon of the iminium group. Therefore, it seemed possible that these TSs may actually link the starting materials to an intermediate in which the C−C bond is fully formed but with negligible formation of the C−N bond. The C−N separation of 3.08 Å in **TS13-E-*trans*** is closer to the sum of the van der Waals' radii for C and N (3.25 Å) than it is to the length of the full C−N bond (1.55 Å). Moreover, the arrangement of the hydrogen and carbon atoms around the C7 and C10 carbons belonging to the butadiene moiety indicates that while the C7 carbon atom is changing the hybridization from sp[2] to sp[3] along the C2−C7 bond formation, the C10 carbon atom remains sp[2], in agreement with a C8−C9−C10 allyl cation structure. The N1−C2−C7−C8 dihedral angle at this TS, ca. 54°, shows a syn-clinal arrangement of the N1−C2 and the C7−C8 bonds, which favors the N1−C10 bond formation.

A series of constrained minimizations linking the transition structures to the products along the reaction coordinate was performed with both B3LYP/6-31+G* and MP2/6-31+G* (restricted and unrestricted). Both calculations showed that a relatively flat area of the potential energy surface follows the TS, before the entrance channel to the product well. There is no intermediate between the TS and the products on the DFT potential energy surface.

An intermediate and a second transition structure for the intramolecular aza-Diels−Alder reaction of **13-E**, shown in Figure 6, could be located with HF theory. There are very few geometric differences between **14-E-*trans*** and **TS14-E-*trans***. The C2−C7 bond is fully formed in both structures. The difference between the N1 nitrogen and C10 carbon (3.0 Å) in **14-E-*trans*** is closer to the sum of the van der Waals radii of C and N. Unlike the DFT-optimized TSs, the forming C−N bond (2.7 Å) in **TS14-E-*trans*** is now closer in length to a normal C−N bond. The C10 carbon atom also remains sp[2] hybridized, in agreement with a C8−C9−C10 allyl cation structure.

A representation of the HF and DFT PESs is depicted in Figure 7. Activation energies calculated with HF for intramolecular hetero-Diels−Alder reactions are overestimated by approximately 13.0 kcal/mol for the iminium systems. B3LYP single-point calculations were performed on HF geometries of the transition structures and intermediates. The rate-determining step is lowered by 1.1 kcal/mol compared to the original B3LYP optimized structures. However, intermediate structures **14-Z-**

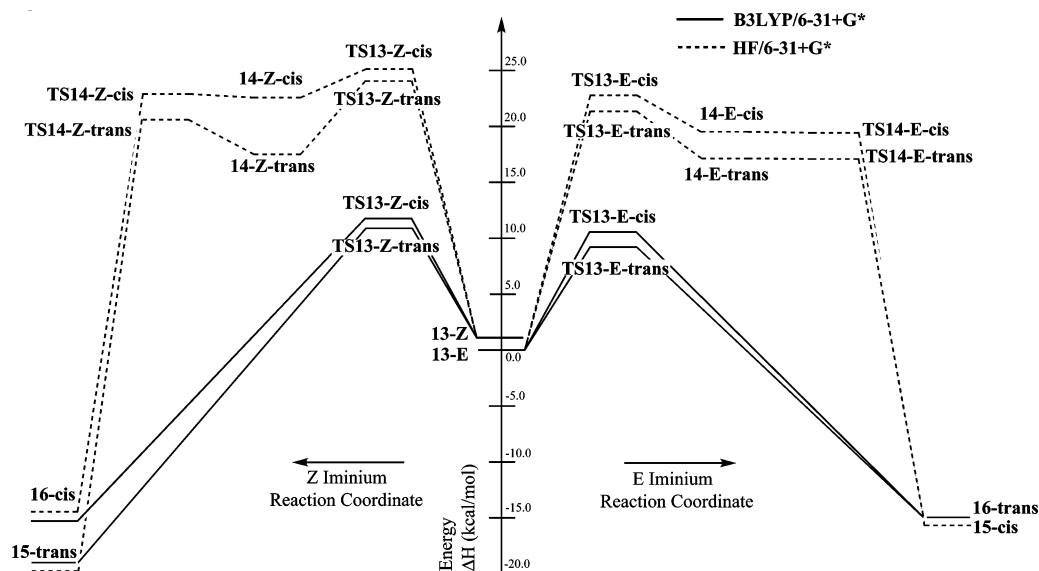(22) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041.

FIGURE 7. Energy profiles for the intramolecular aza-diels−Alder reactions of **13-E** and **13-Z**. HF/6-31+G* predicts stepwise pathways (dashed line), while B3LYP/6-31+G* predicts concerted processes.
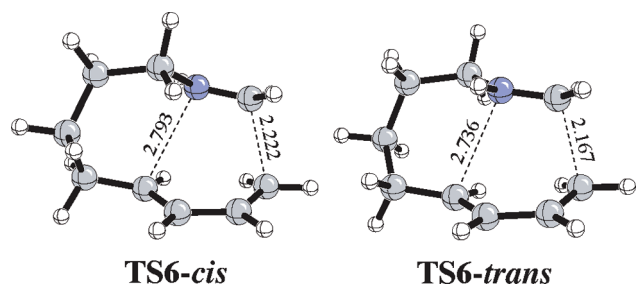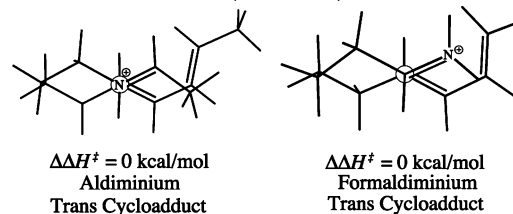

FIGURE 8. B3LYP/6-31+G* transition structures for the intramolecular hetero-Diels−Alder reaction of formaldiminium **6**.

trans and **14-E-*trans*** and transition structures **TS14-Z-*trans*** or **TS14-E-*trans*** remained higher in energy than **TS13-Z-*trans*** or **TS13-E-*trans***. Therefore, these structures are artifacts of HF theory. When electron correlation is accounted for, the intermediate is higher in energy than the first transition structure. The compound would preferentially form the cycloadduct in a concerted manner then proceed through a higher intermediate, but the reaction is highly asynchronous, even involving formation of a "para-intermediate" that does not have any appreciable barriers to formation of the second bond.[23]

The enthalpies for the reaction of aldiminium **13-Z** are −20.8 and −16.0 kcal/mol for the *trans* and *cis* cycloadducts, respectively. The geometries of **TS13-Z-*trans*** and **TS13-Z-*cis*** are presented in Figure 5. The *trans* TS is calculated to have a lower activation barrier (8.5 kcal/mol). The geometry of the TS is highly asynchronous and shows once again negligible bond formation about the N1−C10 bond. Constrained minimizations along the reaction pathway were also performed for this reaction, and similar to the reaction of **13-E**, no intermediate or stepwise TS could be located with DFT.

For formaldiminium **6**, reaction enthalpies of −33.9 and −37.0 kcal/mol are predicted for the formation of **7-*cis*** and **7-*trans***, respectively. The geometries of **TS6-*cis*** and **TS6-*trans*** are presented in Figure 8. The energetically favored *trans* transition structure is fairly asynchronous. The predicted en-

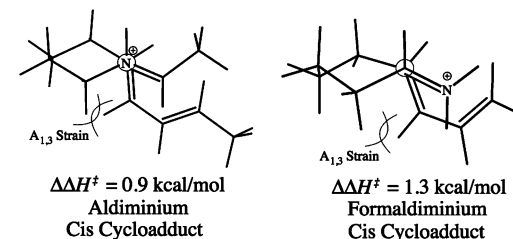(23) Northrop, B. H.; Houk, K. N. *J. Org. Chem.* **2006**, *71*, 3.

FIGURE 9. Newman projections of transition structures for internal iminium dienophiles.

thalpy barrier for the concerted pathway is 3.1 kcal/mol, yielding the *trans* cycloadduct **7-*trans***. The TS of the cycloaddition of **6** involves less asynchronous bond formation than for the aldiminium structure. Both the C7 and C10 carbons are changing hybridization from sp[2] to sp,[3] while the C7 carbon atom remains nearly planar. Unlike the reaction of **13**, no intermediate or stepwise pathways could be located with either HF/6-31+G* and B3LYP/6-31+G* (restricted and unrestricted) on the potential energy surface for the intramolecular aza-Diels−Alder reaction of **6**.

Figure 9 shows Newman projections for transition structures with the butadiene moiety held in an axial conformation. The free energies for *trans* cycloadditions are 0.9−1.5 kcal/mol lower than those for *cis* in the gas phase. The *trans* transition states (**TS13-E-*trans***, **TS13-Z-*trans***, and **TS6-*trans***) minimize 1,3-diaxial strain and gauche interactions about the forming bonds. Grieco and co-workers have observed *trans* selectivity in the intramolecular hetero-Diels−Alder reaction of **1** experi-

SCHEME 8. Computed Stereoselectivities of Hydrocarbon Trienes[24]

X = H, CO₂Me

X = H	55:45
CO₂Me	60:40
CO₂Me•BH₃	60:40
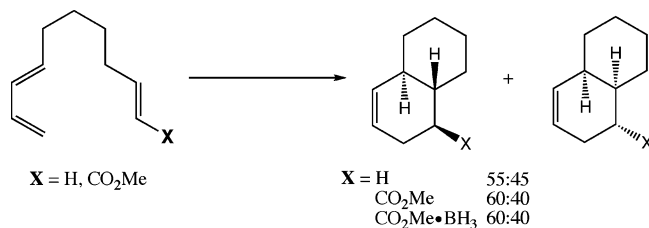
mentally.[3] A 2.5:1 ratio of *trans:cis* adducts is formed in the presence of a 1:1 water/ethanol mixture.

These reactions have similar stereoselectivities as decatrienes (Scheme 8).[24] *trans*-Decalin products are slightly favored for ten-membered rings. This stereochemical outcome originates from a preferred chair conformation only attained when the substituents are equatorial. Calculations on Lewis acid-catalyzed reactions of terminally activated alkenes also showed a large degree of asynchronicity[25] and pronounced diastereoselectivity for the *trans*-fused ring systems.[24] The asynchronicity makes the steric requirements quite different at either of the forming bonds. These resemble the intramolecular aza-Diels−Alder reactions of imines and iminium ions.

Conclusions

Intramolecular hetero-Diels−Alder reactions of iminium and imine dienophiles are predicted to be concerted but to involve highly asynchronous transition states. While asynchronicity in the forming bonds of imine dienophiles depends on the nitrogen position and the approach of the diene-dienophile fragments, asynchronicity in the hetero-Diels−Alder reaction of iminium dienophiles is strongly controlled by the electrophilic carbon of the iminium moiety. No intermediate structures were found with DFT calculations, but surfaces involve para-intermediates— species resembling intermediates but with short lifetimes characteristic of TSs, since there is no barrier to closure of the second bond. Brønsted acid catalysis is predicted to increase the reaction rate by as much as 10^{12} using a dielectric continuum model for water. The preference for the *trans* pathway for reactions involving iminium dienophiles arises from a combination of steric interactions from 1,3-diaxial interactions of the butadiene moiety and gauche interactions about the forming bond. Stereocontrol of the imine cycloadditions is predominantly influenced by the exo-lone-pair effect.

Supporting Information Available: HF and B3LYP optimized Cartesian coordinates and electronic energies (hartrees) for reactants, transition structures, and products, and the full citation for reference 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796.

(25) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297.