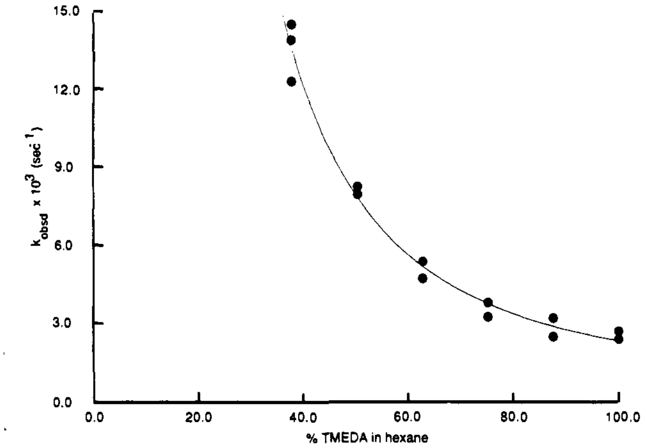
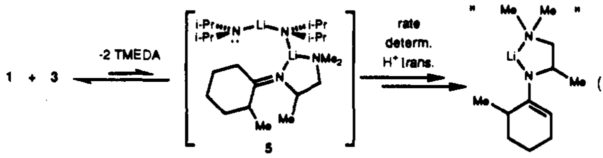


Figure 1. Plot of k_{obsd} versus [TMEDA] in hexane cosolvent for the metalation of imine **3** (0.004 M) by LDA (0.13 M) at 0.0 ± 0.5 °C. The curve depicts the result of an unweighted nonlinear least-squares fit to the general expression $k_{obsd} = k'[\text{TMEDA}]^n + k''$. The adjustable parameter n corresponds to the order in TMEDA (-2.02 ± 0.01). The parameter k'' (0.52 ± 10^{-3}) corresponds to the observed rate constant for the metalation via monomers (eq 1).[10]

DA/hexane mixtures causes essentially complete inhibition of the metalation.[10]

In the context of MNDO calculations we noted that open dimers could provide a viable pathway for reaction of lithium amide dimers without intervening deaggregation.[6,11] We now present such a mechanism as consistent with the rate data (eq 4). Open dimer **5** is certainly not the only possible intermediate; however, despite little precedence for open dimers in the literature prior to 1990,[11] recent spectroscopic,[5,12] computational,[6] and crystallographic[7] support for lithium amide open dimers makes **5** highly plausible. As to the origin of the double TMEDA dissociation, MNDO calculations predicted quite unequivocally that lithium amide open dimers are viable intermediates only when unsolvated on the internal lithium.[6] Moreover, the 8-membered-ring transition state has been shown to be optimal for related internal proton abstractions.[13] We hasten to add that the mechanism depicted in eq 4 is not generally available to **3**; metalation of **3** in THF displays rate behavior consistent with the mechanism specified by eqs 1 and 2.[10]

$$-d[\mathbf{2}]/dt = k'[\mathbf{2}][\text{LDA}][\text{TMEDA}]^{-2} \qquad (3)$$



(4)

In summary, a number of features of the mechanism depicted in eq 4 are without precedent or contrary to conventional wisdom. These include (1) the high lability of TMEDA toward dissociation; (2) a TMEDA-dependent rate acceleration stemming from dissociation of two TMEDA ligands; (3) metalation via an LDA dimer rather than monomer; and (4) promotion of aggregate (relative to monomer) reactivity by a bidentate interaction with the substrate. The observed change in the mathematical form of the rate equation provides an important criterion for invoking participation by internal ligands.[4]

Acknowledgment. We acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility. We thank the National Institutes of Health for direct support of this work.

Supplementary Material Available: Kinetic plots affording reaction orders for metalation of **2** and **3** (2 pages). Ordering information is given on any current masthead page.

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(10) Metalations of **3** in dimethylethylamine—an isostructural analog of TMEDA incapable of bidentate coordination[2]—display the same rate profile and small KIE. These and other studies will be described in due course.

(11) For a calculated open dimer-like transition state, see: Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560.

(12) For additional solution structural studies of open dimers, see: Paquette, L. A.; Bauer, W.; Sivik, M. R.; Bühl, M.; Feigel, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 8776. Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202.

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Tuning Exo/Endo Stereoselectivity in Ene Reactions

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We have reported the startling observation that a lone pair on a dienophile can have a very large effect on the exo/endo selectivity in Diels-Alder reactions.[1] The large preference for the transition structure with the nitrogen lone pair exo was attributed to a repulsive interaction between the π-system of butadiene and the nitrogen lone pair in the endo transition structure. We have found that related electrostatic interactions in other reactions may be attractive or repulsive, depending on the charge densities at various sites in the transition structures.

The ene reaction of propene with formaldehyde imine can proceed with CC bond formation and hydrogen transfer to the nitrogen or with CN bond formation and hydrogen transfer to the methylene group of formaldehyde imine. Experimentally, there are far fewer examples of ene reactions with imines as the enophile than alkenes or carbonyls.[2] These types of reactions typically fall into three groups: (1) reactions of imines with electron-withdrawing groups attached to the nitrogen[3] such as reaction A; (2) retro-ene reactions of amines[4] such as reactions B and C; and (3) intramolecular ene reactions of *N*-acyl imines with CN bond formation (D)[5] (Scheme I).

Ab initio molecular orbital calculations were performed on the simplest parent reaction with GAUSSIAN 90.[6] The geometries of the reactants and transition structures were optimized using restricted Hartree-Fock theory and the 3-21G and 6-31G* basis sets.[7,8] Harmonic vibrational frequency calculations were performed to confirm the nature of all stationary points. Energies of each RHF/6-31G* stationary point were calculated with inclusion of electron correlation using second-order Møller-Plesset theory[9] and the 6-31G* basis set. The CHELPG program was

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0002-7863/93/1515-790$04.00/0

Scheme I

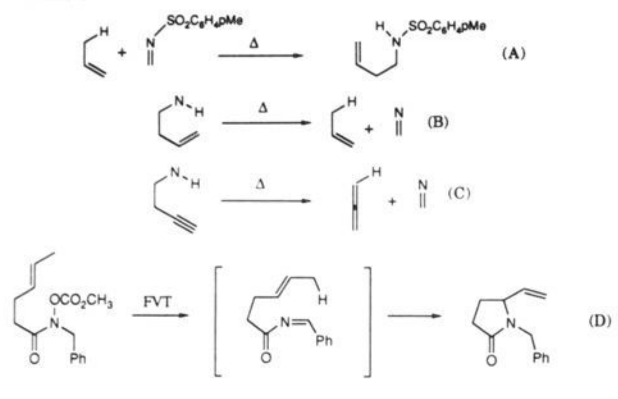

Table I. Activation Energies of the Transition Structures of the Ene Reaction of Propene and Imine[a]

structure	RHF/ 3-21G	RHF/ 6-31G*	MP2/ 6-31G*	MP2/ 6-31G*+ZPE
TS exo CC	40.0	56.1	27.8	27.7
TS endo CC	43.4	59.0	30.7	30.7
TS exo CN	57.5	71.3	39.1	39.1
TS endo CN	50.0	65.3	31.0	30.4

[a] Exo/endo indicates the orientation of the lone pair with respect to the central carbon of the ene. CC/CN indicates the nature of the forming bond.

used to calculate the atomic charges on the basis of electrostatic potentials.[10]

There are two transition structures for each ene reaction, where the lone pair on nitrogen can be exo or endo with respect to the central carbon of propene. The RHF/6-31G* transition structures for CC bond formation are shown in Figure 1. The activation energies are given in Table I. The geometries of these transition structures are similar to the geometry of the propene–ethylene transition structure.[11] At the MP2/6-31G*//RHF/6-31G*+ZPE level, the activation energy for the endo transition structure is 27.7 kcal/mol, 3.0 kcal/mol lower in energy than the exo transition structure. An electrostatic attraction between the nitrogen lone pair and the partially positive central carbon of the ene is responsible. The atomic charges of the CC transition structures, shown in Figure 1, indicate that the central carbon has a partial positive charge in both transition structures. This charge development is characteristic of most ene transition structures[11] since the enophile is electrophilic. This charge development has been proposed for a variety of catalyzed ene reactions,[12] since electron-donating groups are often required at the 2-position of the ene in order for the reaction to proceed. From the top views of these transition structures in Figure 1, the lone pair in the endo transition structure is ideally located to interact with the central carbon of the ene with good staggering about the forming CC bond. In the exo transition structure, some rotation takes place about the forming CC bond to improve the interaction of the lone pair with the central carbon of the ene or to reduce the H(N)–central carbon interaction. This is an example of an attractive electrostatic interaction dictating the stereochemical outcome of a reaction.

This ene reaction of an electrophilic imine is predicted to be faster than the parent ene reaction of propene with ethylene. At the MP2/6-31G*//RHF/6-31G*+ZPE level of theory, the parent ene reaction has an activation energy of 31.5 kcal/mol,[11] which is 3.8 and 0.8 kcal/mol higher in energy than the endo and exo imine CC transition structures, respectively.

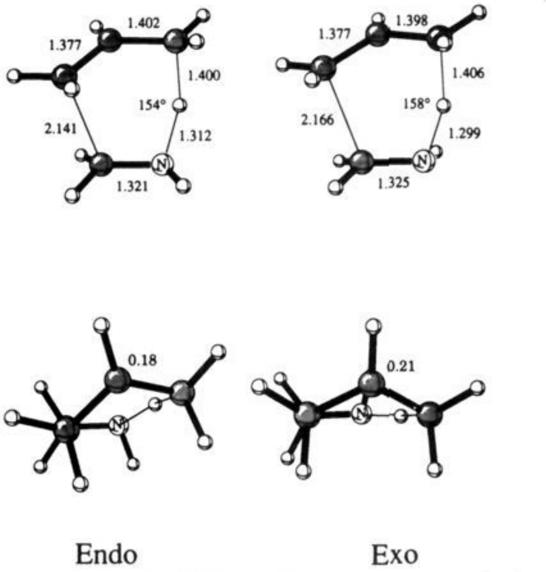

Figure 1. Two views of the RHF/6-31G* transition structures for the ene reaction of propene and formaldehyde imine which led to the formation of primary amines. The CHELPG atomic charge at the central carbon of the ene is given in the lower view of each transition structure.

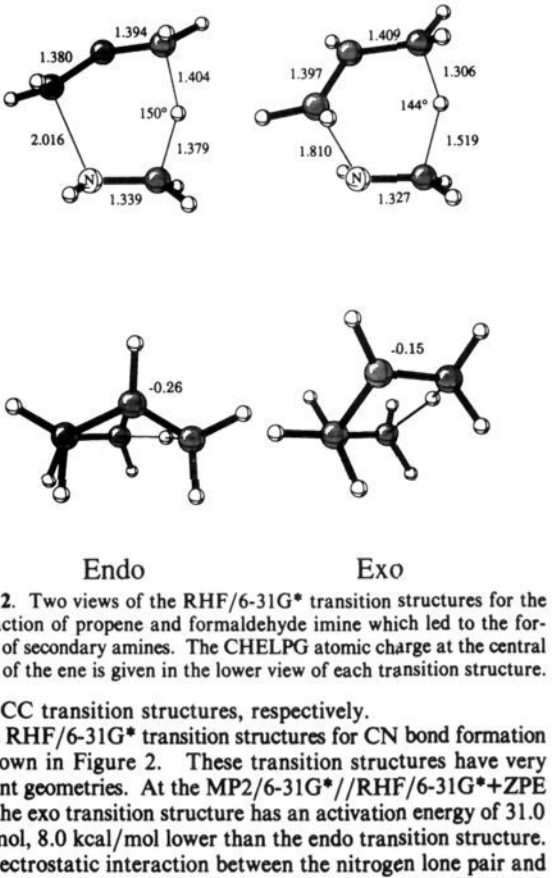

Figure 2. Two views of the RHF/6-31G* transition structures for the ene reaction of propene and formaldehyde imine which led to the formation of secondary amines. The CHELPG atomic charge at the central carbon of the ene is given in the lower view of each transition structure.

The RHF/6-31G* transition structures for CN bond formation are shown in Figure 2. These transition structures have very different geometries. At the MP2/6-31G*//RHF/6-31G*+ZPE level, the exo transition structure has an activation energy of 31.0 kcal/mol, 8.0 kcal/mol lower than the endo transition structure. The electrostatic interaction between the nitrogen lone pair and the central carbon of the ene is now repulsive. The CHELPG atomic charges, shown in Figure 1, indicate that the central carbon has a partial negative charge in both transition structures. This is an example of an inverse electron demand ene reaction. In the exo transition structure the lone pair is oriented away from the central carbon of the ene. In the endo transition structure the lone pair rotates away from the central carbon of the ene but is still oriented toward the central carbon of the ene. This repulsive interaction causes the forming CN bond to lengthen from 1.810 Å in the exo transition structure to 2.016 Å in the endo transition structure (Figure 1). The net result is a large destabilization of

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the endo transition structure. This exo preference is similar to the exo preference for the Diels–Alder reaction of butadiene with formaldehyde imine.[1] In the endo transition structure, the nitrogen lone pair interacts with the internal carbon of the diene which is adjacent to the terminus that forms the CN bond. CHELPG charges indicate that a partial negative charge (−0.28 eu) develops on the internal carbon in the endo transition structure,[1b] making the interaction with the nitrogen lone pair repulsive. In the Diels–Alder reaction of butadiene with formaldehyde imine and in the ene reaction of propene with formaldehyde imine where CN bond formation occurs, stereoselectivity is determined by a repulsive electrostatic interaction, while in the ene reaction of propene with formaldehyde imine where CC bond formation occurs, stereoselectivity is determined by a stabilizing electrostatic interaction.

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Stereoselective Cyclization of Carbene-Derived 1,5-Biradicals

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The stereoselectivity of free radicals has been a subject of considerable interest.[1] With regard to ring closure, attention has traditionally been focused on 1,3- and 1,4-biradicals.[2] Over the past few years, high diastereoselectivities have been observed in photocyclizations of α-arylacetophenones (**1**) and *o*-alkoxybenzophenones (**2**).[3] These reactions involve δ-hydrogen abstraction by the ketone triplets, followed by cyclization of the 1,5-biradical intermediates (Scheme I). The interactions that cause diastereoselectivity can either pre-exist in the biradicals or be created as the substituents on the radical ends approach each other.[3,4] Very recently, we showed that triplet arylcarbenes (**3**) also abstract hydrogen from ortho side chains, generating 1,5-biradicals (**4**).[5] It occurred to us that the hydrogen transfer in **3** could be utilized to deuterate the benzylic site of **4** stereoselectively, depending on the location of deuterium in the carbene precursor (**3a** → (*E*)-**4**; **3b** → (*Z*)-**4**). Steric discrimination caused by the approach of terminal substituents is virtually eliminated in the cyclization of **4** to give **5**, yet we observe substantial diastereoselectivity that can be traced to conformational preferences of **4**.

Scheme I

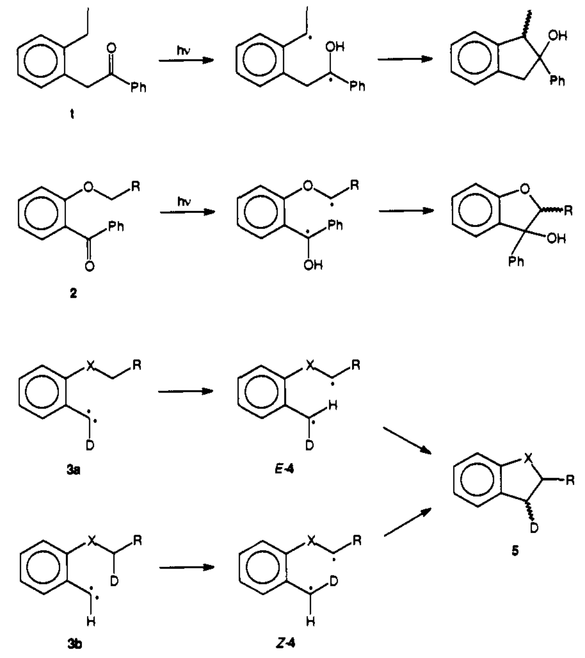
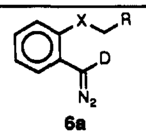
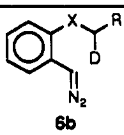


Table I. Deuterium Distributions Obtained from C–H Insertion Reactions of Arylcarbenes with Ortho Side Chains

		 **6a**		 **6b**		
X	R	*trans*-**5**	*cis*-**5**	*trans*-**5**	*cis*-**5**	k_H/k_D
O	Me	79	21			
	Et	75	25	20	80	6.7
	i-Pr	81	19			
	Ph	66	34	33	67	4.0
CH_2	Ph	85	15	10	90	4.6
	$SiMe_3$	58	42	31	69	4.4
	CH_2SiMe_3	65	35			

The α-deuterated diazo compounds **6a** were obtained by H–D exchange, using NaOD–D_2O–dioxane in the cleavage of tosylhydrazone precursors. Side-chain deuterium (**6b**) was introduced in the course of aldehyde synthesis, proceeding from salicylaldehyde (X = O), 2-bromobenzyl bromide (X = CH_2, R = Ph), and (2-bromophenyl)ethyne (X = CH_2, R = $SiMe_3$). Photolyses of **6a,b** (Pyrex, pentane, 20 °C) afforded various derivatives of 2,3-dihydrobenzofuran (X = O) and indan (X = CH_2), which were analyzed by ^2H NMR (Table I). The assignments were confirmed, whenever possible, by cis addition of D_2 to the appropriate benzofurans and indenes. The choice of X and R was limited by our ability to resolve the signals of cis and trans deuterons; insufficient Δδ frustrated our work with X = O, R = *t*-Bu and X = CH_2, R = alkyl.

The data in Table I reveal that the α-deuterium of **6a** prefers the trans position in **5**. Most of the δ-deuterium in **6b** is recovered at C-2 of **5**; large deuterium isotope effects support the abstraction–recombination route to **5**. The (minor) transfer of deuterium, **3b** → (*Z*)-**4**, leads to an excess of *cis*-D in **5**, the distribution being inverse to that observed with **3a**. Our findings are clearly incompatible with an intermediate biradical **4** that rotates freely on both ends. The interconversion of (*E*)-**4** and (*Z*)-**4** is thought to be slow relative to ring closure,[6] given the large rotational barriers of benzyl radicals.[7] On the other hand, rotational equilibration of the side chain will be fast, as indicated by racemization in the case of chiral δ-carbons.[5,8] Two major

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(6) The necessary biradical triplet → singlet intersystem crossing has been proposed to occur along the cyclization reaction coordinate.[3c]

(7) Dorigo, A. E.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 6942 and references therein.