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Diels−Alder Reactions of 4-Alkenylthiazoles: A New Approach to Thiazole Functionalization

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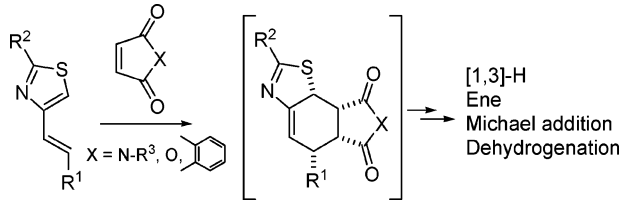

Somewhat unexpectedly, the computed highest occupied molecular orbital (HOMO) energies of some 4-alkenylthiazoles afforded values close to those calculated for the Danishefsky−Kitahara and Rawal dienes. In fact, 4-alkenylthiazoles behave as all-carbon dienes in Diels−Alder reactions with the participation of the formal C−C double bond of the thiazole ring and the side-chain double bond. The reactions with *N*-substituted maleimides, maleic anhydride, and naphthoquinone take place with high levels of stereocontrol to give the corresponding *endo*-cycloadducts in good to excellent yields. Depending on the dienophile, the cycloadduct further transforms under the reaction conditions through either a 1,3-hydrogen shift, dehydrogenation, or an ene reaction or Michael addition with another molecule of dienophile. These unprecedented results open new synthetic perspectives for the functionalization of the thiazole ring.

Introduction

Heteropolycycles are key compounds in the development of modern pharmaceutical chemistry, this being the reason why the design of amenable synthetic approaches for the synthesis of new heterocyclic systems is still an attractive challenge.[1] Because its simplicity and efficiency, the Diels−Alder reaction provides a valuable method for the regioselective and stereoselective preparation of these types of compounds.[2] Besides the hetero Diels−Alder methodology,[3] another alternative to generate heterocyclic rings fused to a carbocyclic system by using the Diels−Alder approach consists of the use of conjugated dienes in which one of the double bonds is embedded in a heteroaromatic nucleus, that is, alkenyl-substituted heterocycles.[4] In general, alkenyl-substituted aromatic heterocycles, and their benzoderivatives, undergo Diels−Alder reactions with the concourse of the diene moiety that includes the side-chain double bond (extra-annular addition).[4] In most cases the latter way of interacting is preferred to that involving the proper heteroaromatic nucleus (intra-annular addition) as far as this nucleus contains in turn a conjugated diene arrangement.[4b] Nevertheless, the reactivity of these dienes is highly influenced not only by the nature and number of heteroatoms but also by the aromatic character of the heterocycle;[5] this approach is successful, with a few exceptions,[6] only with π-excessive five-membered

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(1) Dewick, P. M. In *Medicinal Natural Products. A Biosynthetic Approach*, 2nd ed.; Wiley: Chichester, U.K., 2002.

(2) (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, pp 315−399. (b) Fringuelli, F.; Taticchi, A. *The Diels−Alder Reaction*−Selected Practical Methods; Wiley: Chichester, U.K., 2002. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(3) Boger, D. L.; Weinreb, S. M. In *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(4) (a) Sepúlveda-Arques, J.; Abarca-González, B.; Medio-Simón, M. *Adv. Heterocycl. Chem.* **1995**, *63*, 339−401. (b) Fringuelli, F.; Taticchi, A. *The Diels−Alder Reaction*−Selected Practical Methods; Wiley: Chichester, U.K., 2002; pp 56−64.

(5) Fringuelli, F.; Taticchi, A. *The Diels−Alder Reaction*−Selected Practical Methods; Wiley: Chichester, U.K., 2002; pp 40−41.

(6) (a) Jones, G.; Rafferty, P. *Tetrahedron Lett.* **1978**, *19*, 2731−2734. (b) Jones, G.; Rafferty, P. *Tetrahedron* **1979**, *35*, 2027−2033.

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heterocyclic derivatives.[4a] However, some disadvantages of this methodology are the competition of Michael additions, ene reactions, [2 + 2] cycloadditions and polymerizations with the desired Diels−Alder reaction.[4a]

The involvement of some types of alkenyl heterocycles as dienes in Diels−Alder reactions has been previously studied.[7a−m] Thus, 1-substituted 2- and 3-vinylpyrroles react easily with electron-deficient dienophiles to provide dihydro- and tetrahydroindoles with further 1,3-hydrogen migration in the corresponding cycloadduct.[7a,b] The 2- and 3-vinylindoles also react with carbodienophiles to produce carbazoles.[7c−f] Recently, Lovely and co-workers[7g] and Romo and co-workers[7h,i] have developed new methods for access to a spirobicyclic system, related to those found in marine alkaloids such as palau'amines, based on the Diels−Alder reaction of vinylimidazoles. The [4 + 2] cycloaddition reactions of vinylfurans and vinylbenzofurans with dimethyl acetylenedicarboxylate, tetracyanoethylene, α,β-unsaturated ketones, quinones, and maleimides have been also investigated.[4,7j,k] Vinylthiophenes are less reactive than the analogous furans, reacting only with the most reactive dienophiles.[7l,m] Moreover, they behave somewhat differently from furans and in many cases the corresponding cycloadducts are unstable and undergo cheleotropic extrusion of sulfur.[8]

We were interested, for both synthetic and mechanistic reasons, in [4 + 2] cycloadditions in which *alkenylthiazoles* participate by means of the diene moiety that includes the side-chain double bond. Surprisingly, this type of process has not been previously investigated, probably due to the general acceptance that thiazoles have a low reactivity in Diels−Alder reactions caused by their considerable aromatic stabilization.[9]

At first sight, 4-alkenylthiazoles (**1**) may be synthesized from easily available starting materials. Our retrosynthetic analysis for the synthesis of these compounds is shown in Scheme 1. Thus, thiazoles **1** could be prepared from α-chloroketone **2** and thioamide **3** through a Hantzsch synthesis.[10] The α-chloroketone **2** could be derived from (3-chloroacetonylidene)triphenylphosphorane (**4**) and the corresponding aldehyde by means of a Wittig reaction. Finally, the alkylidenephosphorane **4** could be easily obtained from 1,3-dichloroacetone by previously described procedures.[11]

Herein, we disclose our findings in the Diels−Alder reaction of 4-alkenylthiazoles with different dienophiles such as *N*-substituted maleimides, maleic anhydride, or naphthoquinone. Contrary to expectations, 4-alkenylthiazoles are versatile dienes

SCHEME 1. Retrosynthetic Analysis of 4-Alkenylthiazoles 1

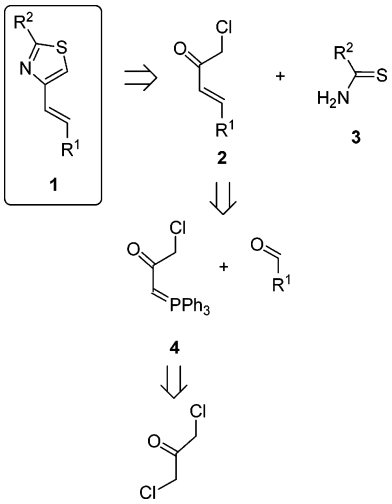
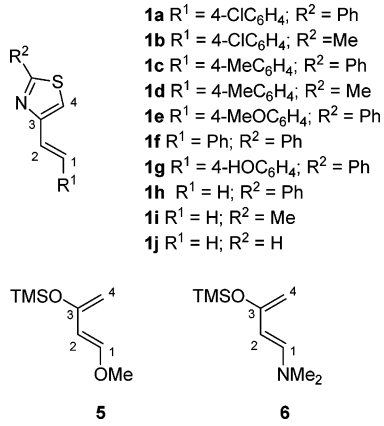


CHART 1. Structures of 4-Alkenylthiazoles 1a−j and Dienes 5 and 6



in this type of process, forming new heteropolycyclic systems in their reactions with the above-mentioned dienophiles in good to excellent yields. The reactions take place with a high degree of stereoselection to give the *endo* cycloadducts. The results here disclosed are interesting not only from the synthetic point of view but also because they open new routes to the functionalization of the thiazole ring.

Results

Synthesis of the Starting Materials. We selected as starting materials the 4-alkenylthiazoles **1a**−**e** shown in Chart 1, each of them containing an aromatic substituent attached to the β-position of the alkenylic side chain. This structural feature was chosen on the basis of the easier accessibility of the starting α-chloroketones (**2a**−**c** in Scheme 2) prepared by the Wittig reaction of alkylidenephosphorane **4** and 4-chlorobenzaldehyde, tolualdehyde, or 4-methoxybenzaldehyde (see Supporting Information). α-Chloroketones **2a**−**c** were allow to react with thiobenzamide (**3a**) or thioacetamide (**3b**) in EtOH under reflux to give thiazoles **1a**−**e** in high yields (87−95%) (Scheme 2).

HOMO Values. The qualitative application of the frontier molecular orbital (FMO) theory has frequently proved of value for predicting the results of Diels−Alder reactions.[7d] Dienes possessing substituents capable of donating their electron density into the conjugated π-system display high reactivity in Diels−

(7) (a) Jones, R. A.; Marriott, M. T. P.; Rosenthal, W. P.; Sepúlveda-Arques, J. *J. Org. Chem.* **1980**, *45*, 4515−4519. (b) Xiao, D.; Ketcha, D. M. *J. Heterocycl. Chem.* **1995**, *32*, 499−503. (c) Noland, W. E.; Wann, S. R. *J. Org. Chem.* **1979**, *44*, 4402−4410. (d) Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368−5374. (e) Pindur, U.; Kim, M.-H.; Rogge, M.; Massa, W.; Molinier, M. *J. Org. Chem.* **1992**, *57*, 910−915. (f) Back, T. G.; Pandyra, A.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 3299−3302. (g) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, *7*, 965−992. (h) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535−1538. (i) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679−1682. (j) Marrocchi, A.; Minuti, L.; Taticchi, A.; Scheeren, H. W. *Tetrahedron* **2001**, *57*, 4959−4965. (k) Le Strat, F.; Vallete, H.; Toupet, L.; Maddaluno, J. *Eur. J. Org. Chem.* **2005**, 5296−5305. (l) Scully, J. F.; Brown, E. V. *J. Am. Chem. Soc.* **1953**, *75*, 6329−6330. (m) Moody, C. J.; Rees, C. W.; Tsoi, S. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 915−920.

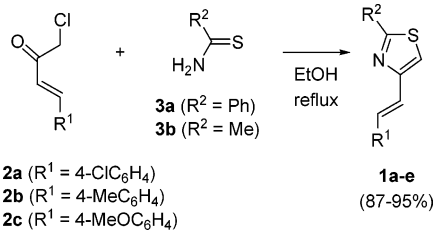
(8) Corral, C.; Lissavetzky, J.; Manzanares, I. *Synthesis* **1997**, 29−31.

(9) *Thiazole and its Derivatives*; Metzger, J. V., Ed.; Wiley: New York, 1979.

(10) (a) Hantzsch, A. R.; Weber, J. H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118−3132. (b) Schwarz, G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, pp 332−333.

(11) Hudson, R. F.; Chopard, P. A. *J. Org. Chem.* **1963**, *28*, 2446−2447.

SCHEME 2. Synthesis of 4-Alkenylthiazoles 1a−e through Hantzsch Synthesis



Alder reactions of normal electronic demand.[12] According to the FMO theory this phenomenon, reflected experimentally in higher reaction rates, is due to the increase of the diene's highest occupied molecular orbital (HOMO) energy and, consequently, the smaller $HOMO_{diene}-LUMO_{dienophile}$ gap (LUMO = lowest unoccupied molecular orbital).[13] The reactivity of dienes increases not only with the number of electron-releasing substituents but also when they are placed in adequate positions to cause a cooperative effect. Thus, the Danishefsky−Kitahara and Rawal dienes, with electron-donor substituents at 1- and 3-positions, display high reactivity in [4 + 2] cycloaddition reactions.[14−16] The enhanced reactivity of both dienes has been rationalized on the basis of FMO theory, which also afforded accurate semiquantitative predictions of the behavior of other dienes and dienophiles in [4 + 2] cycloadditions.[17] We have also used this methodology for investigating the relative reactivity of dienes **1f**−**j** (Chart 1),[18] and here we compare the results with those obtained for Danishefsky−Kitahara (**5** in Chart 1) and Rawal dienes computed at the same level of theory. With the aim of simplifying the calculations, we substituted the *tert*-butyldimethylsilyl group of Rawal's diene by the simpler Me_3Si (**6** in Chart 1). The HOMO energies were obtained through single-point Hartree−Fock (HF) calculations with the 6-31G basis set at the B3LYP/6-31G geometries, as this procedure has been shown to provide more accurate orbital energies than the B3LYP level.[16h]

Although it is expected that the s-trans conformation of these dienes (**1f**−**j**, **5**, **6**) is lower in energy than the s-cis conformation, we have optimized only the s-cis form as this is the reactive conformation. Moreover, the trends in reactivity should be the same for the s-trans and the s-cis series. The computed B3LYP/6-31G geometries of dienes **1f**−**j**, **5**, and **6** are shown in Figure 1.

The s-cis conformers of **5** and **6** are twisted out of planarity by 26.9° and 25.2°, whereas the s-cis forms of dienes **1f**−**j** showed, in all the computed cases, a planar geometry. In Table 1 we summarize the HOMO energies and the $2p_z$ eigenvectors of the HOMOs of all these dienes.

The HOMO energies point out that dienes **1f**−**j**, 4-alkenylthiazoles, should behave as activated dienes in [4 + 2] cycloaddition reactions of normal electronic demand. Whereas dienes **1h**−**j** probably should show a reactivity comparable to **5**, dienes **1f** and **1g** are predicted to be more reactive as their HOMO energies are closer to that of **6**. By comparison of the HOMO energies of **1f** and **1h**, it is apparent that the presence of the phenyl group at C1 contributes to a considerable increase in the HOMO energy and improves the desired reactivity. Therefore, dienes possessing a structure similar to that of **1f**, such as those used in the experimental work (**1a**−**e**), are predicted to participate efficiently in Diels−Alder reactions with electron-deficient dienophiles.

Reactions of 4-Alkenylthiazoles 1a−e with *N*-Substituted Maleimides. First, we tested the reaction of thiazole **1a** with *N*-phenylmaleimide (NPM). In toluene at 20 °C, no reaction took place. At higher temperatures, 140 °C, we obtained a mixture of two compounds (each one being a racemate), *endo*-**7a** and **8a** (Scheme 3 and Table 2, entry 1), which were isolated as result of complete diastereoselection. While *endo*-**7a** comes from the Diels−Alder reaction of both reagents followed by a 1,3-hydrogen migration, compound **8a** is the result of the reaction of one molecule of **1a** with two molecules of maleimide. This species **8a** could be isolated as the major product when **1a** and NPM were allowed to react in a 1:4 ratio without solvent at 120 °C (Table 2, entry 3). Under these reaction conditions, **8a** was obtained in 66% yield along with *endo*-**7a** (21%). We investigated whether in these processes **8a** would form by the reaction of *endo*-**7a** with another molecule of NPM. However, after these two latter compounds were heated together in toluene solution at 140 °C for 24 h, they were recovered unaltered (Scheme 3). Finally, just a solvent change from toluene to acetonitrile allowed the formation of *endo*-**7a** as a single product in excellent yield when the reaction was conducted at 120 °C in a sealed tube for 48 h (Table 2, entry 4).

This latter solvent and temperature combination was utilized in the rest of the reactions of 4-alkenylthiazoles **1a**−**e** with *N*-phenyl-, *N*-methyl-, and *N*-ethylmaleimide (Table 2, entries 4−16). In all the cases the corresponding endo adducts, *endo*-**7a**−**m**, were obtained as the major products in excellent yields, although in some cases accompanied by small quantities of *exo*-**7** and **8** (Table 2, entries 7−15).

Alternatively, when the reactions of 4-alkenylthiazoles **1a, 1c**, and **1e** with NPM were conducted under milder conditions

(12) For reviews see (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753−786. (b) Jorgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093−2102.

(13) (a) Fukui, K. *Tetrahedron Lett.* **1965**, *6*, 2009−2015. (b) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57−64. (c) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17−22. (d) Woodward, R. B.; Hoffmann, R. In *The Conservation of the Orbital Theory*; Verlag Chemie: Weinheim, Germany, 1970. (e) Fleming, I. In *Frontier Orbitals and Organic Chemical Reactivity*; Wiley: New York, 1976. (f) Houk, K. N. In *Pericyclic Reactions*; Lehr, R. E., Marchand, A. P., Eds.; Academic Press: London, 1977; Vol. 2, p 181. (g) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361−369.

(14) (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808. (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400−406. (c) Banville, J.; Brassard, P. J. *Chem. Soc., Perkin. Trans. 1* **1976**, 1852−1856. (d) Danishefsky, S.; Singh, R. K.; Gammill, R. B. *J. Org. Chem.* **1978**, *43*, 379−380. (e) Ibuka, T.; Mori, Y.; Inubushi, Y. *Tetrahedron Lett.* **1976**, *17*, 3169−3172.

(15) For 1,3-bis(dimethylamino) dienes, see (a) Gompper, R.; Sobotta, R. *Tetrahedron Lett.* **1979**, *20*, 921−924. (b) Gompper, R.; Heinemann, U. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 216−217.

(16) For 1-amino-3-siloxy dienes, see (a) Smith, A. B., III; Wexler, B. A.; Tu, C.-Y.; Konopelski, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1308−1320. (b) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1992**, *57*, 4098−4103. (c) Schlessinger, R. H.; Pettus, T. R. R.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1994**, *59*, 3246−3247. (d) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252−5253. (e) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039−3052. (f) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165−7166. (g) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1999**, *121*, 9562−9573. (h) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045−8047.

(17) (a) Sustmann, R.; Schubert, R. *Tetrahedron Lett.* **1972**, *13*, 2739−2742. (b) Sustmann, R.; Schubert, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 840. (c) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182−3189. (d) Kawasaki, I.; Sakaguchi, N.; Khadeer, A.; Yamashita, M.; Ohta, S. *Tetrahedron* **2006**, *62*, 10182−10192. (e) Sheng, Y.; Leszczynski, J. *Tetrahedron* **2006**, *62*, 7014−7020. (f) Landreau, C.; Janvier, P.; Julienne, K.; Meslin, J. C.; Deniaud, D. *Tetrahedron* **2006**, *62*, 9226−9231. (g) See also ref 16h.

(18) 4-Alkenylthiazoles **1f**−**i** have not been described previously in the literature. For the preparation of thiazole **1j**, see Schilling, C. L., Jr.; Mulvaney, J. E. *Macromolecules* **1968**, *1*, 445−451.

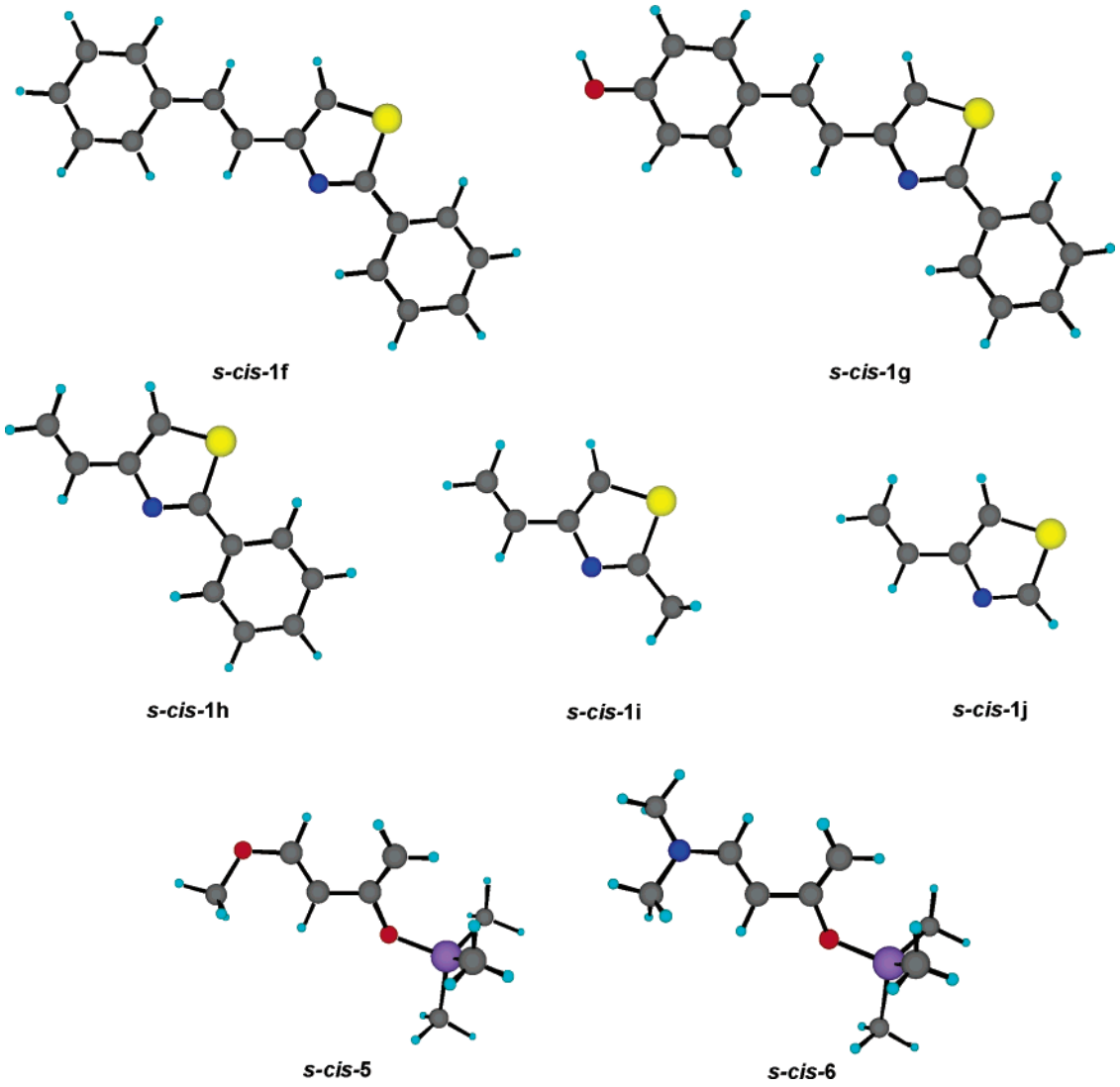


FIGURE 1. Computed B3LYP/6-31G geometries of dienes **1f**−**j**, **5**, and **6** in their respective *s-cis* conformations.

TABLE 1. HOMO Values for 4-Alkenylthiazoles 1f−j and Dienes 5 and 6 in Their s-cis Conformation

		$2p_z$ coefficients			
diene	eigenvalue (eV)	C1	C2	C3	C4
s-cis-**1f**	−7.47	−0.21	−0.21	0.17	0.25
s-cis-**1g**	−7.35	−0.20	−0.22	0.15	0.24
s-cis-**1h**	−8.01	−0.19	−0.12	0.22	0.28
s-cis-**1i**	−8.41	−0.26	−0.19	0.25	0.30
s-cis-**1j**	−8.65	−0.28	−0.20	0.25	0.29
s-cis-**5**	−8.13[a]	−0.22	−0.23	0.21	0.34
s-cis-**6**	−7.18[b]	−0.19	−0.30	0.14	0.29

[a] −8.08 in ref 16h. [b] −7.18 in ref 16h.

(refluxing acetonitrile) some of them yielded mixtures of *endo*-**7** and *endo*-**9** in different ratios and overall yields depending on the R substituent (Scheme 4). Compounds *endo*-**9** are just the expected initial cycloadducts, from which compounds *endo*-**7** derive by subsequent 1,3-hydrogen migration. While **1a** showed no conversion at all under these reaction conditions, **1e** displayed the highest overall yields leading to *endo*-**9m** in 50% yield as a single diastereomer (racemic mixture). These results indicate an increase of the reactivity along the series R = Cl, Me, OMe (Scheme 4). The higher reactivity of **1e** compared to **1a** and **1c** agrees with its higher electron density as well as with the HOMO energy value of *s-cis*-**1g**, the highest one among all the computed HOMO energies of these thiazoles (Table 1). As presumed, when *endo*-**9m** was stirred at 120 °C for 36 h, it clearly isomerized to compound *endo*-**7m** in 85% yield, by recovering the aromaticity of the thiazole ring through the expected 1,3-hydrogen shift (Scheme 4).

Many reactions are accelerated by Lewis acid catalysts, and the catalyzed reactions show also increased regio- and stereoselectivities over the uncatalyzed reactions.[19] The reaction between **1a** and NPM was investigated under Lewis acid catalysis (Et_2AlCl, $BF_3{\cdot}Et_2O$ or $ZnCl_2$), but unfortunately, poorer conversions and lower yields were obtained compared to the reactions conducted under thermal conditions.

We investigated also the reaction of **1a** with NPM under controlled microwave irradiation (270−440 W). Microwave radiation is an alternative to conventional heating for introducing energy into reactions[20] and a number of Diels−Alder reactions

(19) (a) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094−4096. (b) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1990; pp 50−53. (c) Fringuelli, F.; Taticchi, A. *The Diels−Alder Reaction*−Selected Practical Methods; Wiley: Chichester, U.K., 2002; pp 99−142.

SCHEME 3. Reactions of 4-Alkenylthiazoles 1a−e with *N*-Substituted Maleimides

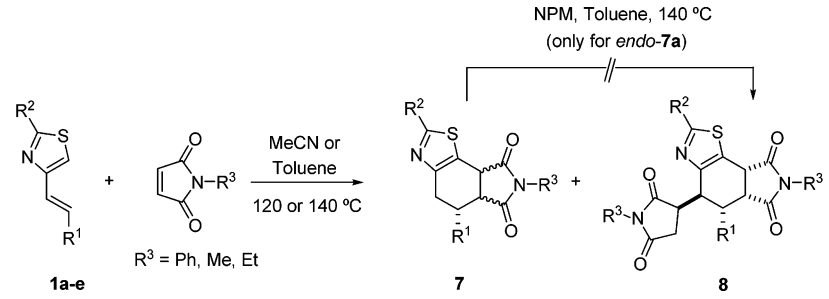
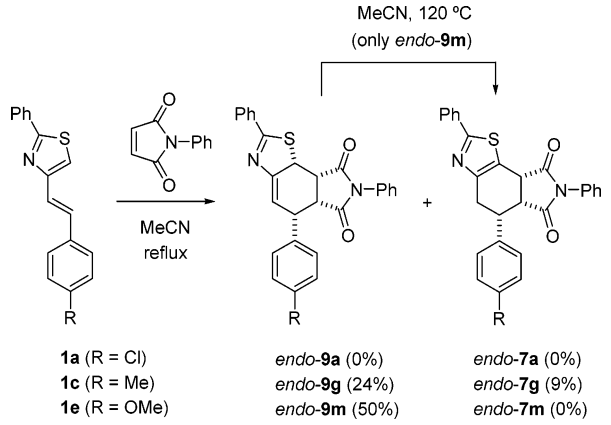


TABLE 2. Reactions between 4-Alkenylthiazoles 1a−e and *N*-Substituted Maleimides

entry	compd	R^1	R^2	R^3	solvent	*endo*-**7** (%)	*exo*-**7** (%)	**8** (%)
1	**a**	4-ClC_6H_4	Ph	Ph	toluene[a]	46	0	18
2	**a**	4-ClC_6H_4	Ph	Ph	—[b,c]	25	0	42
3	**a**	4-ClC_6H_4	Ph	Ph	—[c,d]	21	0	66
4	**a**	4-ClC_6H_4	Ph	Ph	MeCN[e]	94	0	0
5	**b**	4-ClC_6H_4	Ph	Me	MeCN[e]	92	0	0
6	**c**	4-ClC_6H_4	Ph	Et	MeCN[e]	86	0	0
7	**d**	4-ClC_6H_4	Me	Ph	MeCN[e]	91	0	8
8	**e**	4-ClC_6H_4	Me	Me	MeCN[e]	74	6	0
9	**f**	4-ClC_6H_4	Me	Et	MeCN[e]	88	4	0
10	**g**	4-MeC_6H_4	Ph	Ph	MeCN[e]	80	0	20
11	**h**	4-MeC_6H_4	Ph	Me	MeCN[e]	86	7	0
12	**i**	4-MeC_6H_4	Ph	Et	MeCN[e]	88	7	0
13	**j**	4-MeC_6H_4	Me	Ph	MeCN[e]	74	0	8
14	**k**	4-MeC_6H_4	Me	Me	MeCN[e]	66	8	13
15	**l**	4-MeC_6H_4	Me	Et	MeCN[e]	90	3	0
16	**m**	4-$MeOC_6H_4$	Ph	Ph	MeCN[e]	90	0	0

[a] **1**:maleimide ratio 1:1.3; 140 °C. [b] **1**:maleimide ratio 1:2. [c] Neat; 120 °C. [d] **1**:maleimide ratio 1:4. [e] **1**:maleimide ratio 1:3; 120 °C.

SCHEME 4. Reaction between 4-Alkenylthiazoles 1a, 1c, and 1e and *N*-Phenylmaleimide[a]

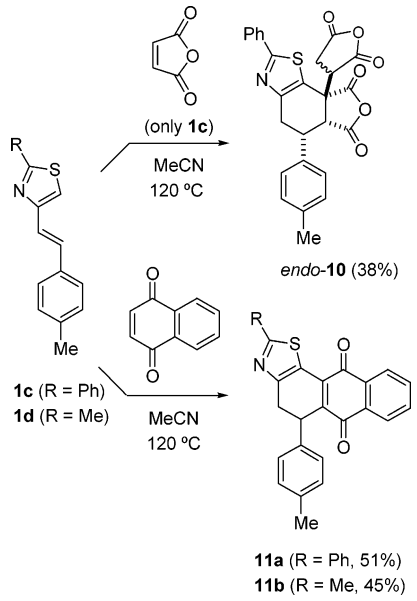


[a] Under milder conditions this reaction gives mixtures of *endo*-**7** and *endo*-**9**. Treatment at 120 °C of *endo*-**9m** leads to *endo*-**7m**.

have been performed with great success under these reaction conditions, especially those requiring the use of high temperatures and long reaction times. However, in our case the use of microwave radiation did not improve the results obtained under thermal conditions since 1:1 mixtures of *endo*-**7a** and **8a** were obtained, albeit in lower overall yields (49−63%).

(20) (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284. (b) Fernández Sainz, Y.; Raw, S. A.; Taylor, R. J. K. *J. Org. Chem.* **2005**, *70*, 10086−10095. (c) Pinto, D. C. G. A.; Silva, A. M. S.; Brito, C. M.; Sandulache, A.; Carrillo, J. R.; Prieto, P.; Díaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2005**, 2973−2986. (d) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *Synlett* **2006**, 1369−1373.

SCHEME 5. Reactions of 4-Alkenylthiazoles 1c,d with Maleic Anhydride and Naphthoquinone



Reactions with Maleic Anhydride and Naphthoquinone. We investigated the reaction of thiazole **1c** with maleic anhydride (Scheme 5). Both reagents were allowed to react in acetonitrile at 120 °C for 48 h, leading to the compound *endo*-**10** in moderate yield and as a single diastereomer (racemic mixture). Compound *endo*-**10** is the result of the reaction of **1c** with 2 equiv of maleic anhydride. No other cycloadducts could be isolated from the reaction mixture.

Finally, we investigated the reactions of thiazoles **1c,d** with naphthoquinone. These reactions took place in acetonitrile at 120 °C for 72 h, leading to **11a,b** in moderate yields (Scheme 5) along with high quantities of recovered starting thiazole (40%).

Configurational Assignments of *endo*-7, *exo*-7, 8, *endo*-9, and *endo*-10. The relative configurational assignment of the four newly formed stereocenters in compounds *endo*-**9** was done by comparison of selected coupling constants in *endo*-**9g** and *endo*-**9m** with those of analogous structures described in the literature.[21] The assignment of the relative configuration of *endo*-**7** and *exo*-**7** was achieved by performing $^1H-^1H$ NOESY experiments (see Supporting Information). Before the measurement of the NOESY spectra, we calculated the B3LYP/6-31+G** optimized structures of *endo*-**7h** and *exo*-**7h** (see Supporting Information). Both minimum energy structures

(21) (a) Lovely, C. J.; Du, H.; Rasika Dias, H. V. *Org. Lett.* **2001**, *3*, 1319−1322. (b) Lovely, C. J.; Du, H.; He, Y.; Rasika Dias, H. V. *Org. Lett.* **2004**, *6*, 735−738.

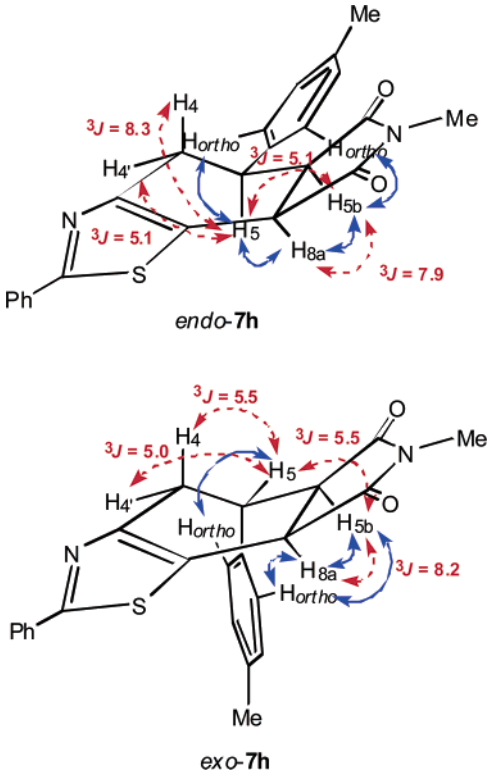


FIGURE 2. Significant NOE effects (blue arrows) and coupling constants (red arrows) for *endo*-**7h** and *exo*-**7h**.

display a distorted boat conformation of the central cyclohexene ring in which the 4-tolyl substituent placed at C_5 may be situated in an equatorial or an axial arrangement (*endo*-**7h** or *exo*-**7h**, respectively) depending on the absolute configuration of this carbon atom (Figure 2). NOESY data revealed the spatial proximity of protons H_5/H_{8a}, H_{5b}/H_{8a}, H_{ortho}/H_5, and H_{ortho}/H_{5b} for *endo*-**7h** and that of protons H_{ortho}/H_{8a}, H_{5b}/H_{8a}, H_{ortho}/H_5, and H_{ortho}/H_{5b} for *exo*-**7h** (blue arrows in Figure 2). These NOE contacts agree with the energy-minimized structures of both diastereomers since all the protons involved are less than 4.5 Å apart. This assignment was unambiguously confirmed by X-ray analysis of *endo*-**7c** (see Supporting Information). Selected $^1H-^1H$ coupling constants calculated from the ^1H NMR spectra of *endo*-**7h** and *exo*-**7h** are depicted in Figure 2. Finally, the relative configuration of the five newly formed stereogenic centers in compounds **8** was assigned following the X-ray structure determination of **8j** (see Supporting Information).

The relative configurational assignment of *endo*-**10** was done by comparison of its ^1H NMR data (in particular the coupling constants between protons H_5/H_4, H_5/H_4', and H_5/H_{5b}) with those of *endo*-**7h** (Figure 3, in red). A long-range coupling between H_4' and H_{5b} was also observed due to a zigzag arrangement of these two protons (Figure 3, in blue).[22] The relative configuration of the remaining stereogenic carbon atom at the pendent oxolane-2,5-dione ring remains unknown.

Discussion

In spite of the general acceptance that thiazoles may have low reactivity in Diels−Alder reactions due to their considerable

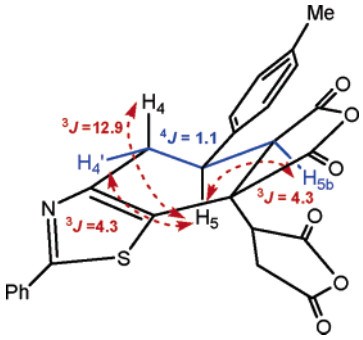


FIGURE 3. Selected coupling constants (in red) of *endo*-**10** supporting the relative configurational assignment. A long-range coupling due to a zigzag arrangement between protons $H_{4'}$ and H_{5b} was observed (in blue).

aromatic stabilization,[9] the computed energies for the HOMOs of 4-alkenylthiazoles **1f−j** revealed that they should be prone to participate as reactive dienes in this type of process (see above). In fact, when they were allowed to react with classical dienophiles such as maleimides, maleic anhydride, or naphthoquinone, we could isolate the corresponding cycloadducts although in most cases they were involved in subsequent transformations. Thus, mixtures of *endo*-**7**, *exo*-**7**, and **8** were obtained when *N*-substituted maleimides were used as dienophiles and the reactions were conducted above 100 °C (Scheme 3). Under milder reaction conditions (Scheme 4), cycloadducts *endo*-**9** were isolated as single compounds (*endo*-**9m**, racemate) or as mixtures (*endo*-**7g**/*endo*-**9g**, both racemates). The treatment of *endo*-**7a** with an excess of NPM did not lead to **8a** but instead the starting material was recovered unaltered (Scheme 3). From all these results, it is clear that **7** and **8** may be formed from a common intermediate, that is, the primary Diels−Alder adduct **9** (Scheme 6). Spontaneous, formal 1,3-hydrogen shift may produce compounds **7** or, alternatively, an ene reaction with another molecule of maleimide may give compounds **8**. Both processes, the 1,3-hydrogen migration and the ene reaction, caused the rearomatization of the thiazole ring.

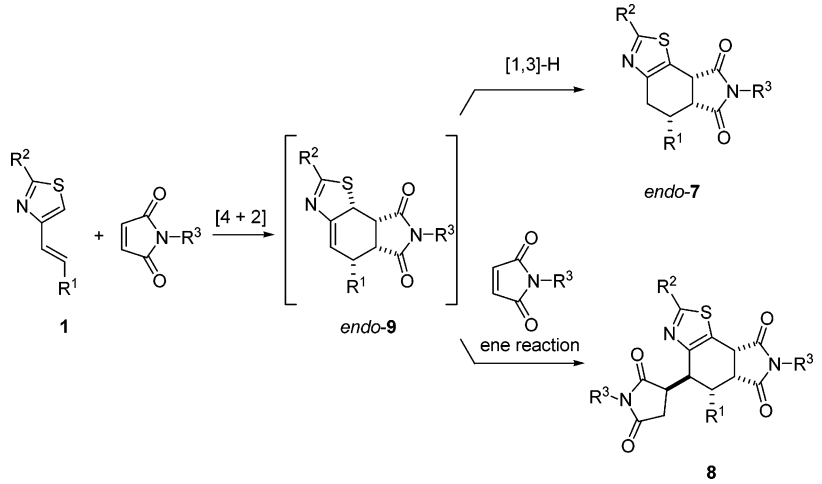
The Diels−Alder reactions of **1a−e** with maleimides take place in a highly stereocontrolled manner. This assertion is substantiated by the relative configurational assignment of *endo*-**7**, **8**, and *endo*-**9**, which were isolated as single or major diastereomers (racemic mixtures). Probably, the favorable secondary frontier orbital interactions control the stereochemistry of the endo Diels−Alder transition state, before the formal 1,3-hydrogen shift or the ene reaction takes place, leading to **7** or **8**. This assertion would be valid only when the subsequent hydrogen shift or ene reaction are not rate-limiting steps. The same behavior has been previously observed in the reaction of other alkenylheterocycles with maleimides.[7d]

In none of these reactions was it possible to detect either a betaine intermediate originating from a stepwise process or a Michael-type adduct. This experimental observation and the high levels of stereocontrol of the Diels−Alder reaction point to a concerted mechanism.[23] However, the lower temperature required when the reactions are run in acetonitrile compared to that in toluene seems to indicate that the transition state is highly polarized. Taking into account these facts, we consider that the

(22) Jackman, L. M.; Sternhell, S. In *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1969; pp 334−341.

(23) (a) Tietze, L. F.; Bratz, M.; Machinek, R.; v. Kiedrowski, G. *J. Org. Chem.* **1987**, *52*, 1638−1640. (b) Shimizu, T.; Murakami, H.; Kamigata, N. *J. Org. Chem.* **1999**, *64*, 8489−8494.

SCHEME 6. Proposed Mechanism for Rationalizing the Formation of Compounds *endo*-7 and 8 from 4-Alkenylthiazoles 1 and *N*-Substituted Maleimides



first step of the sequence yielding **9** is a concerted $HOMO_{diene}$−$LUMO_{dienophile}$-controlled Diels−Alder process. The relative configuration of **8** indicates that the subsequent ene reaction takes place endo-stereoselectively.

The reaction of 4-alkenylthiazole **1c** with maleic anhydride parallels that with maleimides in the first step, leading to the corresponding [4 + 2] cycloadduct through an endo approach. The resulting product would add to a second molecule of maleic anhydride in a Michael-type fashion to give compound *endo*-**10**.

The formation of **11** may be explained through a Diels−Alder reaction of **1c,d** with naphthoquinone with subsequent 1,3-hydrogen shift and dehydrogenation of the *p*-benzoquinone ring. The last step would be favored by the presence of the naphthoquinone in the reaction mixture, acting as an oxidant.[7e,24]

Conclusions

In spite of the general acceptance that thiazoles, due to their considerable aromatic character, may have low reactivity in [4 + 2] cycloadditions, the computed HOMO energies for 4-alkenylthiazoles predict their participation as activated dienes in this type of process of normal electronic demand, as these energy values are close to those of Danishefsky−Kitahara and Rawal dienes. Thus, contrary to some expectations, 4-alkenylthiazoles **1a**−**e** have been demonstrated to behave as reactive all-carbon dienes in Diels−Alder reactions. Their reactions with *N*-substituted maleimides and maleic anhydride take place in a highly stereocontrolled manner to give the corresponding endo cycloadducts, which further transform through either a 1,3-hydrogen shift or an ene reaction or Michael addition with another molecule of dienophile. Additionally, the reaction of **1c,d** with naphthoquinone leads to the corresponding Diels−Alder adducts, followed by a 1,3-hydrogen shift and partial dehydrogenation of the heteropolycyclic system. These results are unprecedented in the chemistry of substituted thiazoles.

Experimental Section

General Procedure for Synthesis of Thiazoles 1a−e. To a solution of the corresponding α-haloketone **2** (3.0 mmol) in ethanol (50 mL) was added the corresponding thioamide **3** (3.0 mmol), and the reaction mixture was stirred under reflux for 5 h. The solvent was removed under reduced pressure and 5% $NaHCO_3$ aqueous solution (50 mL) was added. Then the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried with $MgSO_4$, the solvent was removed, and the residue was purified by silica-gel column chromatography.

4-[(*E*)-2-(4-Chlorophenyl)ethenyl]-2-phenylthiazole (1a). AcOEt/hexane (1:5) was used as eluent (R_f = 0.49); yield 87%; mp 102−105 °C (colorless prisms, $CHCl_3/Et_2O$); IR (Nujol) 1494, 1442, 1091, 1001, 978, 821, 755, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.09 (d, 1H, J = 15.9 Hz), 7.17 (s, 1H), 7.33 (d, 2H, J = 8.6 Hz), 7.44−7.50 (m, 5H), 7.55 (d, 1H, J = 15.9 Hz), 8.00−8.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 115.7 (d), 121.9 (d), 126.8 (2 d), 127.9 (2 d), 129.0 (2 d), 129.1 (2 d), 130.3 (d), 130.4 (d), 133.5 (s), 133.6 (s), 135.7 (s), 154.8 (s), 168.3 (s); MS (EI, 70 eV) *m*/*z* (rel int) 299 (M^+ + 2, 20), 298 (M^+ + 1, 18), 297 (M^+, 53), 296 (21), 194 (45), 159 (33), 158 (22), 149 (52), 121 (100), 115 (79), 104 (38). Anal. Calcd for $C_{17}H_{12}ClNS$ (297.80): C, 68.56; H, 4.06; N, 4.70; S, 10.77. Found: C, 68.21; H, 4.23; N, 4.79; S, 10.62.

Reaction between 4-Alkenylthiazole 1a and *N*-Phenylmaleimide without Solvent: Synthesis of Cycloadducts *endo*-7a and 8a (see Table 2, entry 3). A mixture of alkenylthiazole **1a** (0.10 g; 0.34 mmol) and NPM (0.23 g; 1.34 mmol) was stirred at 120 °C for 4 h. After cooling, the residue was purified by silica-gel chromatography by use of 1:3 → 1:1 AcOEt/hexane as eluent.

(5*R,5a*R**,8a*S**)-5-(4-Chlorophenyl)-2,7-diphenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-7a).** R_f = 0.13 in 1:3 AcOEt/hexane; yield 21%; mp 250−251 °C (colorless prisms, $CHCl_3/Et_2O$); IR (Nujol) 1782, 1704, 1495, 1191, 1169, 1107, 1091, 790, 763, 745, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (dd, 2H, J = 5.8 and 1.4 Hz), 3.83 (dt, 1H, J = 5.8 and 5.4 Hz), 3.91 (dd, 1H, J = 8.1 and 5.4 Hz), 4.49 (dt, 1H, J = 8.1 and 1.4 Hz), 6.81 (d, 2H, J = 7.2 Hz), 7.15 (d, 2H, J = 8.7 Hz), 7.26 (d, 2H, J = 8.7 Hz), 7.33−7.38 (m, 3H), 7.47−7.49 (m, 3H), 7.98−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.7 (t), 39.5 (d), 41.5 (d), 45.8 (d), 121.8 (s), 126.1 (2 d), 126.5 (2 d), 128.78 (2 d), 128.79 (d), 129.06 (2 d), 129.07 (2 d), 129.8 (2 d), 130.5 (d), 131.0 (s), 133.3 (s), 133.5 (s), 138.1 (s), 152.2 (s), 169.1 (s), 173.7 (s), 175.0 (s). MS (EI, 70 eV) *m*/*z* (rel int) 472 (M^+ + 2, 39), 471 (M^+ + 1, 30), 470 (M^+, 100), 345 (34), 323 (73), 198 (31). Anal. Calcd for $C_{27}H_{19}ClN_2O_2S$ (470.97): C, 68.86; H, 4.07; N, 5.95; S, 6.81. Found: C, 68.77; H, 3.82; N, 5.88; S, 6.74.

(4*R,5*S**,5a*S**,8a*R**)-5-(4-Chlorophenyl)-4-[(3*S**)-2,5-dioxo-1-phenylpyrrolidin-3-yl]-2,7-diphenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (8a).** R_f = 0.06 in 1:3 AcOEt/

(24) Partial or full dehydrogenation of cycloadducts resulting from the reaction of dienes with quinones is well documented; see (a) Tominaga, Y.; Lee, M. L.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 967−972. (b) Noland, W. E.; Konkel, M. J.; Tempesta, M. S.; Cink, R. D.; Powers, D. M.; Schlemper, E. O.; Barnes, C. L. *J. Heterocycl. Chem.* **1993**, *30*, 183−192.

hexane); yield 66%; mp 255−257 °C (colorless prisms, $CHCl_3$/Et_2O); IR (Nujol) 1710, 1495, 1184, 760, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (dd, 1H, J = 17.8 and 6.0 Hz), 2.58 (dd, 1H, J = 17.8 and 9.5 Hz), 3.29−3.37 (m, 2H), 3.87 (dd, 1H, J = 7.8 and 4.2 Hz), 4.47 (dt, 1H, J = 11.4 and 2.4 Hz), 4.56 (dd, 1H, J = 7.8 and 2.1 Hz), 7.09−7.12 (m, 2H), 7.28−7.55 (m, 15H), 7.70−7.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.0 (t), 38.0 (d), 41.2 (d), 42.8 (d), 44.3 (d), 45.7 (d), 125.3 (s), 126.2 (2 d), 126.5 (2 d), 126.9 (2 d), 128.4 (d), 128.89 (2 d), 128.94 (3 d), 129.1 (2 d), 129.2 (2 d), 130.8 (d), 131.0 (s), 131.1 (2 d), 132.2 (s), 132.7 (s), 134.2 (s), 135.5 (s), 151.7 (s), 169.9 (s), 173.5 (s), 174.2 (s), 175.1 (s), 178.1 (s). MS (EI, 70 eV) *m*/*z* (rel int) 645 (M^+ + 2, 25), 644 (M^+ + 1, 22), 643 (M^+, 50), 471 (42), 470 (38), 469 (100). Anal. Calcd for $C_{37}H_{26}ClN_3O_4S$ (644.14): C, 68.99; H, 4.07; N, 6.52; S, 4.98. Found: C, 68.73; H, 4.03; N, 6.87; S, 5.04.

Reaction between 4-Alkenylthiazoles 1a−e and *N*-Substituted Maleimides in Acetonitrile: General Procedure for Synthesis of Compounds *endo*-7, *exo*-7, and 8 (see Table 2, entries 4−16). To a solution of the corresponding 4-alkenylthiazole 1 (0.75 mmol) in acetonitrile (10 mL) was added the appropriate maleimide (2.25 mmol). The reaction mixture was kept at 120 °C in a sealed tube for 48 h. The solvent was removed and the residue was purified by silica-gel chromatography.

(5*R,5a*R**,8a*S**)-5-(4-Chlorophenyl)-2,7-diphenyl-4,5,5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-7a).** AcOEt/hexane (1:2) was used as eluent (R_f = 0.20); yield 94% (for spectroscopic and analytical data see above).

(5*R,5a*R**,8a*S**)-5-(4-Chlorophenyl)-7-methyl-2-phenyl-4,5,-5a,8a-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-7b).** AcOEt/hexane (1:2) was used as eluent (R_f = 0.17); yield 92%; mp 188−190 °C (colorless prisms, $CHCl_3$/Et_2O); IR (Nujol) 1781, 1714, 1495, 1436, 1331, 1285, 1109, 1092, 1016, 802, 761, 728, 684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.77 (s, 3H), 3.24 (ddd, 1H, J = 16.3, 8.8, and 1.6 Hz), 3.34 (dd, 1H, J = 16.3 and 5.0 Hz), 3.63 (dt, 1H, J = 8.8 and 5.0 Hz), 3.72 (dd, 1H, J = 8.0 and 5.0 Hz), 4.33 (d, 1H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.7 Hz), 7.28 (d, 2H, J = 8.7 Hz), 7.44−7.46 (m, 3H), 7.93−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.7 (q), 29.2 (t), 39.3 (d), 41.7 (d), 46.0 (d), 122.20 (s), 126.40 (2 d), 128.6 (2 d), 129.0 (2 d), 129.4 (2 d), 130.4 (d), 133.1 (s), 133.3 (s), 138.3 (s), 152.3 (s), 168.7 (s), 174.8 (s), 175.8 (s). MS (EI, 70 eV) *m*/*z* (rel int) 410 (M^+ + 2, 40), 409 (M^+ + 1, 21), 408 (M^+, 100), 323 (31), 283 (87), 198 (46), 185 (30), 184 (47). Anal. Calcd for $C_{22}H_{17}ClN_2O_2S$ (408.90): C, 64.62; H, 4.19; N, 6.85; S, 7.84. Found: C, 64.16; H, 4.22; N, 6.88; S, 7.94.

General Procedure for the Preparation of Compounds *endo*-9. *N*-Phenylmaleimide (0.13 g; 0.72 mmol) was added to a solution of thiazole **1** (0.24 mmol) in acetonitrile (15 mL). The reaction mixture was stirred under reflux for 96 h. The solvent was removed and the residue purified by silica-gel chromatography.

(5*R,5a*R**,8a*S**,8b*R**)-5-(4-Methylphenyl)-2,7-diphenyl-5,5a,-8a,8b-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-9g).** AcOEt/hexane (1:2) was used as eluent (R_f = 0.12); yield 24%; mp 145−147 °C (colorless prisms, $CHCl_3$/Et_2O); IR (Nujol) 1713, 1563, 1175, 964, 722, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 3.53 (dd, 1H, J = 8.4 and 6.0 Hz), 3.71 (m, 1H), 3.80 (t, 1H, J = 8.0 Hz), 4.84 (dt, 1H, J = 7.4 and 2.9 Hz), 6.77 (t, 1H, J = 3.8 Hz), 7.06−7.09 (m, 2H), 7.21 (d, 2H, J = 8.0 Hz), 7.25−7.35 (m, 5H), 7.42−7.45 (m, 2H), 7.48−7.51 (m, 1H), 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1 (q), 43.1 (d), 43.4 (d), 45.0 (d), 49.3 (d), 118.1 (d), 126.3 (2 d), 128.4 (2 d), 128.5 (d), 128.6 (2 d), 128.7 (2 d), 128.9 (2 d), 129.2 (2 d), 131.3 (s), 132.1 (d), 132.7 (s), 135.3 (s), 137.0 (s), 159.3 (s), 173.1 (s), 173.9 (s), 174.0 (s). MS (EI, 70 eV) *m*/*z* (rel int) 451 (M^+ + 1, 26), 450 (M^+, 100), 345 (32), 303 (64), 302 (35), 277 (78), 276 (38), 174 (33), 198 (42), 173 (34), 91 (35). Anal. Calcd for $C_{28}H_{22}N_2O_2S$ (450.55): C, 74.64; H, 4.92; N, 6.22; S, 7.12. Found: C, 74.42; H, 4.87; N, 6.48; S, 7.27.

(5*R,5a*R**,8a*S**,8b*R**)-5-(4-Methoxyphenyl)-2,7-diphenyl-5,-5a,8a,8b-tetrahydropyrrolo[3,4-*g*]benzothiazole-6,8-dione (*endo*-9m).** AcOEt/hexane (1:1) was used as eluent (R_f = 0.16); yield 50%; mp 204−206 °C (colorless prisms, $CHCl_3$/Et_2O); IR (Nujol) 1712, 1514, 1250, 1178, 1030, 825, 727, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (dd, 1H, J = 8.4 and 6.0 Hz), 3.71−3.74 (m, 1H), 3.81−3.85 (m, 4H), 4.87 (dt, 1H, J = 7.5 and 3.1 Hz), 6.75 (t, 1H, J = 3.8 Hz), 6.94 (d, 2H, J = 8.7 Hz), 7.07−7.09 (m, 2H), 7.27−7.35 (m, 5H), 7.42−7.51 (m, 3H), 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 42.8 (d), 43.4 (d), 45.0 (d), 49.3 (d), 55.2 (q), 113.8 (2 d), 118.3 (d), 126.3 (2 d), 128.4 (2 d), 128.5 (d), 128.7 (2 d), 128.9 (2 d), 129.8 (2 d), 130.3 (s), 131.4 (s), 132.1 (d), 132.7 (s), 158.7 (s), 159.3 (s), 173.1 (s), 173.9 (s), 174.1 (s). MS (EI, 70 eV) *m*/*z* (rel int) 467 (M^+ + 1, 18), 466 (M^+, 48), 294 (51), 293 (100), 292 (57), 190 (33), 173 (60), 147 (42), 145 (30), 121 (58). Anal. Calcd for $C_{28}H_{22}N_2O_3S$ (466.55): C, 72.08; H, 4.75; N, 6.00; S, 6.87. Found: C, 71.68; H, 4.87; N, 5.68; S, 7.01.

(5*R,5a*R**,8a*S**)-8a-(2,5-Dioxo-3-oxolanyl)-5-(4-methylphenyl)-2-phenyl-5,5a-dihydro-4*H*-furo[3,4-*g*]benzothiazole-6,8-dione (*endo*-10).** A solution of thiazole **1c** (0.20 g; 0.72 mmol) and maleic anhydride (0.22 g; 2.16 mmol) in acetonitrile (10 mL) was kept at 120 °C in a sealed tube for 48 h. The solvent was removed and the residue was purified by silica-gel chromatography by use of AcOEt → 2:1 AcOEt/MeOH as eluent (R_f = 0.12 in 2:1 AcOEt/MeOH); yield 38%; mp 247−249 °C (colorless prisms, MeCN); IR (Nujol) 1776, 1702, 1299, 1231, 956, 722 cm^{-1}; ^1H NMR (CD_3CN) δ 2.36 (s, 3H), 2.81 (dd, 1H, J = 17.6 and 6.5 Hz), 2.90 (dd, 1H, J = 17.6 and 5.0 Hz), 3.17 (dd, 1H, J = 16.2 and 12.9 Hz), 3.32 (ddd, 1H, J = 16.2, 4.3, and 1.1 Hz), 3.38 (dt, 1H, J = 12.9 and 4.3 Hz), 3.91 (dd, 1H, J = 6.5 and 5.0 Hz), 4.39 (dd, 1H, J = 4.3 and 1.1 Hz), 7.22 (d, 2H, J = 8.0 Hz), 7.39 (d, 2H, J = 8.0 Hz), 7.49−7.52 (m, 3H), 7.95−7.98 (m, 2H); ^{13}C NMR (CD_3CN) δ 21.4 (q), 29.1 (t), 32.7 (t), 39.5 (d), 49.1 (d), 50.4 (d), 54.5 (s), 125.8 (s), 127.7 (2 d), 129.2 (2 d), 130.3 (2 d), 130.7 (2 d), 132.3 (d), 134.4 (s), 137.96 (s), 138.04 (s), 157.7 (s), 170.7 (s), 170.8 (s), 174.0 (s), 174.1 (s), 174.2 (s). MS (EI, 70 eV) *m*/*z* (rel int) 473 (M^+, 8), 401 (17), 373 (24), 303 (24), 302 (100). Anal. Calcd for $C_{26}H_{19}NO_6S$ (473.50): C, 65.95; H, 4.04; N, 2.96; S, 6.77. Found: C, 65.62; H, 4.37; N, 2.54; S, 6.97.

General Procedure for Synthesis of Compounds 11. A mixture of the corresponding 4-alkenylthiazoles **1c,d** (0.30 mmol) and naphthoquinone (0.14 g; 0.30 mmol) was dissolved in acetonitrile (5 mL) and kept at 120 °C in a sealed tube for 72 h. The solvent was removed and the residue was purified by silica-gel chromatography.

5-(4-Methylphenyl)-2-phenyl-4,5-dihydroantra[2,1-*d*]thiazole-6,11-dione (11a). Et_2O/hexane (1:5) was used as eluent (R_f = 0.18); yield 51%; mp 254−256 °C (red prisms, $CHCl_3$/Et_2O); IR (Nujol) 1668, 1652, 1592, 1507, 1340, 1300, 1267, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.52−3.62 (m, 2H), 4.86 (dd, 1H, J = 7.8 and 2.8 Hz), 6.99 (d, 2H, J = 8.0 Hz), 7.14 (d, 2H, J = 8.0 Hz), 7.44−7.48 (m, 3H), 7.71−7.76 (m, 2H), 8.02−8.06 (m, 2H), 8.07−8.10 (m, 1H), 8.16−8.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0 (q), 32.2 (t), 36.3 (d), 120.7 (s), 126.5 (d), 126.6 (3 d), 127.1 (2 d), 129.1 (2 d), 129.5 (2 d), 130.7 (d), 131.2 (s), 132.6 (s), 133.48 (d), 133.54 (s), 134.3 (d), 135.0 (s), 137.1 (s), 138.50 (s), 138.54 (s), 157.4 (s), 174.4 (s), 183.1 (s), 183.2 (s). MS (EI, 70 eV) *m*/*z* (rel int) 434 (M^+ + 1, 29), 433 (M^+, 100), 432 (25), 431 (32), 430 (46), 416 (75), 342 (31). Anal. Calcd for $C_{28}H_{19}NO_2S$ (433.52): C, 77.57; H, 4.42; N, 3.23; S, 7.40. Found: C, 77.33; H, 4.63; N, 3.29; S, 7.52.

2-Methyl-5-(4-methylphenyl)-4,5-dihydroantra[2,1-*d*]thiazole-6,11-dione (11b). AcOEt/hexane (1:5) was used as eluent (R_f = 0.16); yield 45%; mp 164−166 °C (red prisms, $CHCl_3$/Et_2O); IR (Nujol) 1655, 1591, 1508, 1335, 1308, 1266, 728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3H), 2.77 (s, 3H), 3.49 (d, 2H, J = 5.4 Hz), 4.80 (t, 1H, J = 5.4 Hz), 6.98 (d, 2H, J = 8.1 Hz), 7.10 (d, 2H, J = 8.1 Hz), 7.70−7.73 (m, 2H), 8.06−8.08 (m, 1H), 8.12−8.15

(m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.5 (q), 21.0 (q), 32.1 (t), 36.2 (d), 120.2 (s), 126.5 (d), 126.6 (d), 127.0 (2 d), 129.5 (2 d), 131.2 (s), 132.5 (s), 133.4 (d), 134.2 (d), 135.0 (s), 137.0 (s), 138.2 (s), 138.6 (s), 156.0 (s), 173.4 (s), 183.1 (s), 183.2 (s). MS (EI, 70 eV) *m*/*z*(rel int) 372 ($M^+ + 1$, 18), 371 (M^+, 100), 280 (47), 139 (24), 91 (25). Anal. Calcd for $C_{23}H_{17}NO_2S$ (371.45): C, 74.37; H, 4.61; N, 3.77; S, 8.63. Found: C, 74.09; H, 4.69; N, 3.87; S, 8.49.

Computational Methods. All calculations were carried out with the Gaussian03[25] suite of programs. The optimizations of dienes were done at the HF/6-31G[26] theoretical level and then with the B3LYP[27] functional by use of the 6-31+G basis set. *Endo*-**7h** and *exo*-**7h** were optimized at the B3LYP/6-31+G** level. Harmonic frequency calculations at each level of theory verified the identity of each stationary point as a minimum and were used to provide an estimation of the zero-point vibrational energies (ZPVE).

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Supporting Information Available: Full characterization of α-chloroketones **2a** and **2c**, thiazoles **1b**−**e**, and compounds *endo*-**7c**−**m**, *exo*-**7e**−**f**, *exo*-**7h**,**i**, *exo*-**7k**,**l**, **8d**, **8g**, and **8j,k**; ^{1}H−^{1}H NOESY spectra of *endo*-**7h** and *exo*-**7h**; crystallographic information files (CIF) for *endo*-**7c** and **8j**; B3LYP/6-31+G** optimized structures of *endo*-**7h** and *exo*-**7h**; and Cartesian coordinates, electronic energy, and first frequency of thiazoles **1f-j** and dienes **5** and **6** optimized at the B3LYP/6-31G theoretical level and of cycloadducts *endo*-**7h** and *exo*-**7h** optimized at the B3LYP/6-31+G** level. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.03; Gaussian, Inc.: Pittsburgh, PA, 2003.

(26) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. In *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986; pp 71−82 and references cited therein.

(27) (a) Parr, R. G.; Yang, W. In *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Bartolotti, L. J.; Fluchichk, K. In *Reviews in Computational Chemistry*; Lipkowitz, K. B., Boyds, D. B., Eds.; VCH Publishers: New York, 1996; Vol. 7, pp 187−216. (c) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974−12980. (d) Ziegler, *T. Chem. Rev*. **1991**, *91*, 651−667.