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Cross-Diels−Alder Reactions of 6-Oxo-1-Sulfonyl-1,6-Dihydropyridine-3-Carboxylates[#]

Marie-Laure Teyssot, Anh-Tuan Lormier, Isabelle Chataigner, and Serge R. Piettre*

Laboratoire des Fonctions Azotées et Oxygénées Complexes, UMR CNRS 6014, IRCOF-Université de Rouen, Rue Tesnières, F-76821 Mont Saint Aignan, France

Serge.Piettre@univ-rouen.fr

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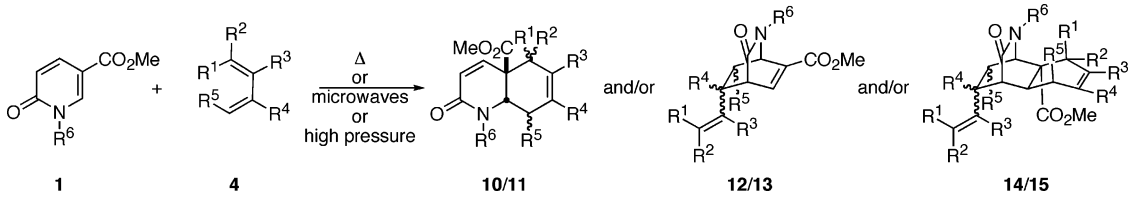

1 **4** **10/11** **12/13** **14/15**

Electron-poor 6-oxo-1-sulfonyl-1,6-dihydropyridine-3-carboxylates **1b**−**d** undergo cross-Diels−Alder reactions with electron-rich dienes **4a**−**f** under hyperbaric conditions, reacting either as dienophiles to yield normal-electron-demand (NED) cycloadducts **10** and/or **11** or as dienes to give inverse-electron-demand (IED) cycloadducts **12** and/or **13**. The latter are converted into **14** and/or **15** through an NED cycloaddition with a second equivalent of electron-rich diene. Acyclic dienes display a propensity to yield NED products, whereas cyclic dienes tend to favor IED cycloadducts. High-pressure activation compares favorably with thermal or microwave activation in terms of both yields and suppression of the transformation of **1** into unreactive pyridines **3**. Whereas the Cope rearrangement from IED to NED occurs under thermal conditions, no evidence of its involvement under high pressure could be detected. These and other data point to similar activation energies for the NED and IED processes under these conditions.

Introduction

More than 80 years after its discovery, the Diels−Alder (DA) reaction still remains one of the most efficient synthetic tools and is probably the best known pericyclic process.[1] In connection with a program aiming to evaluate new scaffolds, we became interested in the dienophilicity of the C2−C3 carbon−carbon double bond of 2-pyridones of the 6-oxo-1,6-dihydropyridine-3-carboxylates **1** variety (Figure 1).[2] Thus, interaction between the C2−C3 double bond in **1** and 1,3-dienes would generate bicyclic products of the type **2** featuring a new quaternary center and a *cis* ring junction. Although compound **1b** was previously reported as a substrate to generate bicyclic products **2b** by way of a thermal interaction with 1,3-dienes,[3] we were also intrigued by the possibility that these substrates might undergo cross-cycloaddition reactions. Indeed, interaction between an electron-rich diene **6** and an electron-poor diene **7** might result in a normal-electron-demand (NED) Diels−Alder reaction to give cycloadduct **8** or an inverse-electron-demand (IED) cycloaddition process to provide **9** (Scheme 1).

In principle, the chemo-, regio, and stereoselectivities of these cross-Diels−Alder reactions are such that intricate mixtures can be produced, thus keeping the process from being synthetically useful. However, selective cross-Diels−Alder reactions have sometimes been observed. Thus, Chou and Hung reported such selective transformations when reacting 2-sulfonylated dienes with classical electron-rich dienes, obtaining either NED or IED cycloadducts with chemo-, regio-, and stereoselectivities depending on the diene.[4] More recently, the group of Liao described exclusive IED processes when reacting masked *o*-benzoquinones with furans.[5]

[#] Dedicated to Professor Léon Ghosez.

(1) (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1990. (b) Oppolzer, W.; Weinreb, S. M.; Boger, D. L.; Roush, W. R. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; pp 315−550. (c) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction*; John Wiley & Sons: Chichester, U.K., 2002. (d) Nicolaou, K. C.; Snyder, S. C.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698.

(2) For better readability, the generic name pyridones is used in this article. In the case of pyridone **1a**, rapid prototropy induces the formation of the more stable 6-hydroxypyridine-3-carboxylate **3a**.

(3) Fujita, R.; Watanabe, K.; Ikeura, W.; Ohtake, Y.; Hongo, H.; Harigaya, Y.; Matsuzaki, H. *Tetrahedron* **2001**, *57*, 8841−8850.

(4) Chou, T.; Hung, S.-C. *J. Org. Chem.* **1988**, *53*, 3020−3027.

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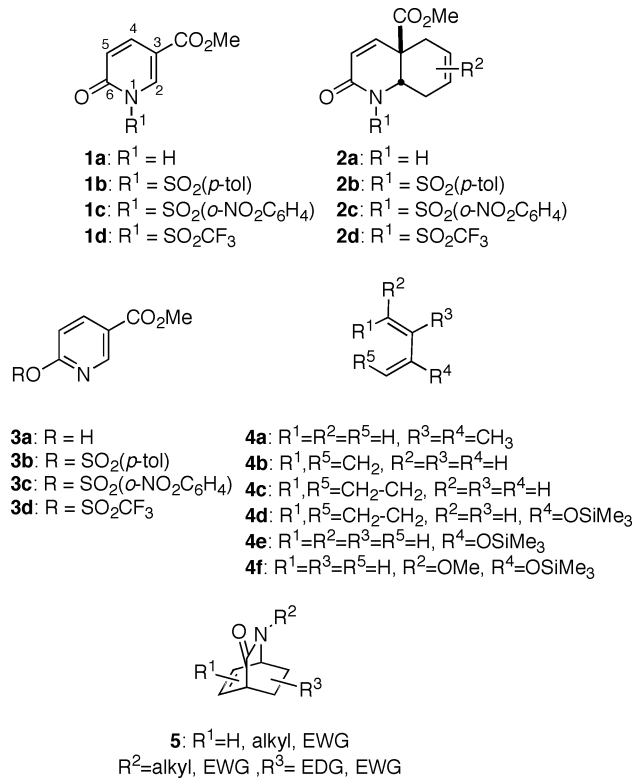
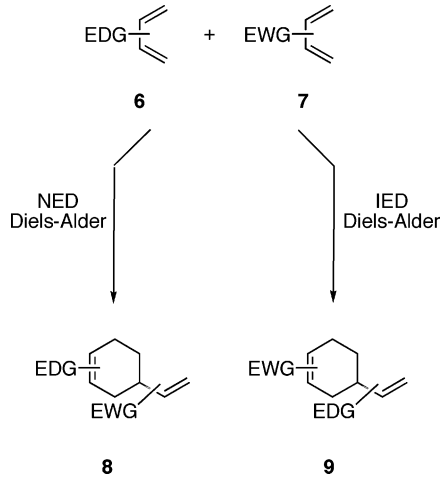


FIGURE 1. Structures of pyridones **1**, pyridines **3**, dienes **4**, and bicyclic products **2** and **5** (EWG = Electron-Withdrawing Group; EDG = Electron-Donating Group).

SCHEME 1



2-Pyridones are peculiar in that, depending on both the nature of the substituent(s) tethered to the nitrogen heterocycle and its (their) position(s), they can behave either as dienophiles in NED cycloadditions or as dienes in IED [4 + 2] processes. The work of Posner, Fujita, and others has established that substituted 2-pyridones react as dienes with both electron-poor and electron-rich dienophiles to generate [2.2.2]-bicyclic adducts of the type **5**.[6] However, thermal interactions of pyridones with electron-rich dienes induce them to behave as dienophiles, thus affording cycloadducts of the type **2**.[7] To date, there has been no report of an IED process resulting from the reaction between electron-poor pyridones and electron-rich dienes.

In this article, we report our results on the reactivity of carbomethoxy-substituted 2-pyridones **1b**−**d**, bearing an *N*-(4-methylphenyl)sulfonyl (*p*-Tos), *N*-(*o*-nitrophenyl)sulfonyl (*o*-Nos), or *N*-(trifluoromethyl)sulfonyl (Tf) group, with electron-rich dienes **4a**−**f** under thermal, microwave, or hyperbaric activation and show that the behaviors of **1** and 2-sulfonylated dienes bear some similarities.

Results

Methyl 1-[(4-Methylphenyl)sulfonyl]-oxo-1,6-dihydropyridine-3-carboxylate (1b). Fujita et al. reported the thermal interaction between pyridone **1b** and 2,3-dimethylbuta-1,3-diene (**4a**) (in *o*-xylene, 180 °C, 48 h), which afforded the expected cycloadduct **10a** in 46% yield, resulting from an NED cycloaddition involving the C2−C3 carbon−carbon double bond of pyridone **1b** as a dienophile (Figure 2; Table 1, entry 1).[3] As reported in the original publication, pyridine **3b**, the product of the mere sulfonyl group transfer from nitrogen to oxygen, was competitively formed and isolated. The harsh reaction conditions led us to seek Lewis acid catalysis as well as other, milder methods of activation.

Microwave radiation has increasingly been used to facilitate organic transformations and usually results in high conversions in short reaction times. This strategy has been effective for [4 + 2] cycloadditions.[8] The highly negative volume of activation of the Diels−Alder reaction led us to consider high pressures as an alternative approach.[9] 2,3-Dimethylbuta-1,3-diene (**4a**), cyclopenta-1,3-diene (**4b**), and cyclohexa-1,3-diene (**4c**) were selected as classical electron-rich dienes. The results obtained from the reaction between **1b** and dienes **4a**−**c** under thermal, microwave, and hyperbaric conditions are summarized in Table 1. Under thermal conditions, catalysis with zinc chloride essentially furnished results at 140 °C identical to those obtained for the uncatalyzed reaction at 180 °C (entries 2 and 3). Activation by microwaves led to poor conversions and mainly afforded pyridine **3b** (entry 4). Neither the addition of Lewis acids nor the use of more polar solvents led to improvement.[10] Conducting the reaction under a pressure of 16 kbar at room

(5) (a) Chen, C.-H.; Rao, P. D.; Liao, C.-C. *J. Am. Chem. Soc.* **1998**, *120*, 13254−13255. (b) Hsieh, M.-F.; Rao, P. D.; Liao, C.-C. *Chem. Commun.* **1999**, 1441−1442. (c) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049−2052.

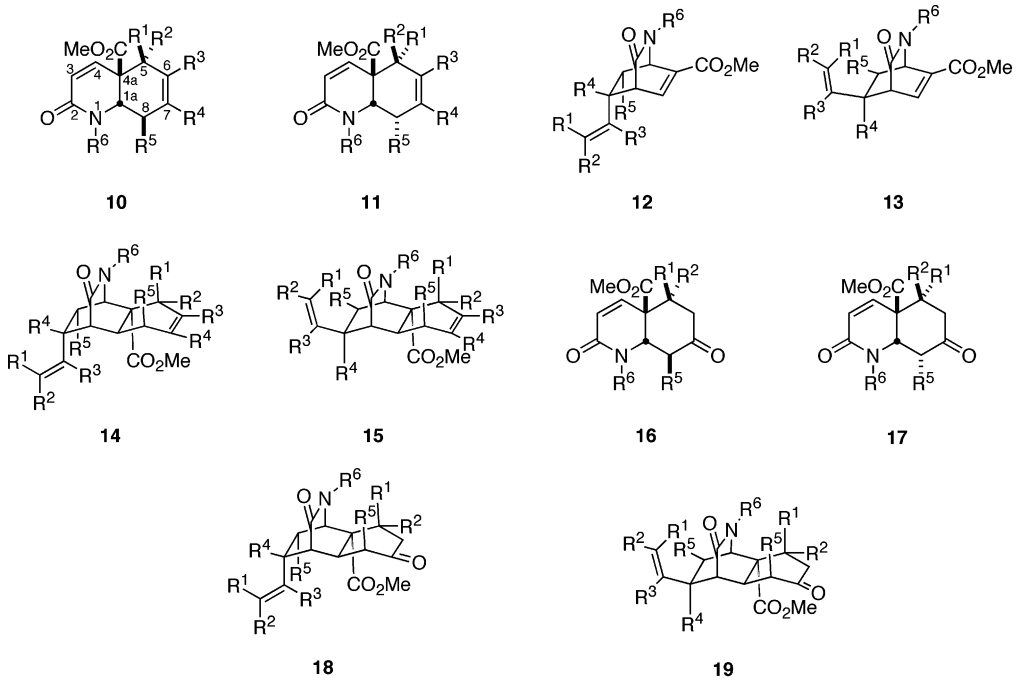
(6) See, for example: (a) Posner, G. H.; Vinader, V.; Afarinkia, K. *J. Org. Chem.* **1992**, *57*, 4088−4097. (b) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111−9171. (c) Fujita, R.; Watanabe, K.; Masuyama, T.; Matsuzaki, H.; Nakano, H.; Okuyama, Y.; Hongo, H. *J. Tohoku Pharm. Un.* **1999**, *46*, 77−81. (d) Okamura, H.; Nagaike, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2000**, *41*, 8317−8321.

(7) See, for instance: (a) Nakano, H.; Date, T.; Okamura, K.; Tomisawa, H.; Hongo, H. *Chem. Pharm. Bull.* **1991**, *39*, 2471−2473. (b) Fujita, R.; Hoshino, M.; Tomisawa, H.; Hongo, H. *Chem. Pharm. Bull.* **2000**, *48*, 1814−1817. (c) Fujita, R.; Hoshino, M.; Tomisawa, H.; Matsuzaki, H.; Hongo, H. *Chem. Pharm. Bull.* **2001**, *49*, 497−500. (d) Fujita, R.; Watanabe, K.; Nishiuchi, Y.; Matsuzaki, H.; Hongo, H. *Chem. Pharm. Bull.* **2001**, *49*, 601−605. (e) Fujita, R.; Watanabe, K.; Ikeura, W.; Ohtake, Y.; Harigaya, Y.; Hongo, H.; Matsuzaki, H. *Tetrahedron* **2001**, *57*, 8841−8850.

(8) (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (c) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.

(9) (a) le Noble, W. J.; Kelm, H. *Angew. Chem., Int. Ed.* **1980**, *19*, 841−856. (b) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1−26. (c) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999−1027. (d) Isaacs, N. S. *Tetrahedron* **1991**, *47*, 8463−8497. (e) Matsumoto, K.; Hamana, H.; Iida, H. *Helv. Chim. Acta* **2005**, *88*, 2033−2234.

(10) Among the Lewis acids were $ZnCl_2$ and EuFOD, and polar solvents such as H_2O, MeOH, DMF, MeCN, AcOEt, and THF were used, without yielding any improvement.



a: $R^1=R^2=R^5=H$, $R^3=R^4=CH_3$, R^6 = *p*-Tos
b: $R^1=R^2=R^5=H$, $R^3=R^4=CH_3$, R^6 = *o*-Nos
c: $R^1=R^2=R^5=H$, $R^3=R^4=CH_3$, R^6 = Tf
d: $R^1,R^5=CH_2$, $R^2=R^3=R^4=H$, R^6 = *p*-Tos
e: $R^1,R^5=CH_2$, $R^2=R^3=R^4=H$, R^6 = *o*-Nos
f: $R^1,R^5=CH_2$, $R^2=R^3=R^4=H$, R^6 = Tf
g: $R^1,R^5=CH_2$-CH_2, $R^2=R^3=R^4=H$, R^6 = *p*-Tos
h: $R^1,R^5=CH_2$-CH_2, $R^2=R^3=R^4=H$, R^6 = *o*-Nos
i: $R^1,R^5=CH_2$-CH_2, $R^2=R^3=R^4=H$, R^6 = Tf
j: $R^1,R^5=CH_2$-CH_2, $R^2=R^3=H$, $R^4=OSiMe_3$, R^6 = *p*-Tos
k: $R^1,R^5=CH_2$-CH_2, $R^2=R^3=H$, $R^4=OSiMe_3$, R^6 = *o*-Nos
l: $R^1,R^5=CH_2$-CH_2, $R^2=R^3=H$, $R^4=OSiMe_3$, R^6 = Tf
m: $R^1=R^2=R^3=R^5=H$, $R^4=OSiMe_3$, R^6 = *p*-Tos
n: $R^1=R^2=R^3=R^5=H$, $R^4=OSiMe_3$, R^6 = *o*-Nos
o: $R^1=R^2=R^3=R^5=H$, $R^4=OSiMe_3$, R^6 = Tf
p: $R^1=R^3=R^5=H$, R^2=OMe, $R^4=OSiMe_3$, R^6 = *p*-Tos
q: $R^1=R^3=R^5=H$, R^2=OMe, $R^4=OSiMe_3$, R^6 = *o*-Nos
r: $R^1=R^3=R^5=H$, R^2=OMe, $R^4=OSiMe_3$, R^6 = Tf

FIGURE 2. Structures of cycloadducts **10**−**13**, biscycloadducts **14** and **15**, and hydrolyzed products **16**−**19**.

temperature, however, resulted in complete conversion within 24 h and the formation of the expected product **10a** (55% after purification) and another oily product (29%) as a single diastereomer (entry 5). Analytical data indicated structure **14a**. NOESY NMR experiments clearly demonstrated the vicinity of H-2, Me-3′ H, and H-1′ cis to Me-3′ (Figure 3). Similar observations were also made between the methyl ester group and Me-3′ H and H-1′ cis to Me-3′. Under these conditions, no trace of 2-tosyloxypyridine 3b was detected in the crude mixture.[11]

No improvement was observed when combining high pressures and a Lewis acid, and the ratio of product **10a** to product **14a** remained unchanged (entries 6 and 7).[12] Careful analysis of the NMR spectra of the crude materials led to no evidence for the formation of either diastereomeric cycloadduct **13a** or biscycloadduct **15a**, derived from **13a**. There was complete facial selectivity in the transformation of IED adduct **12a** into bisadduct **14a**.[13]

The use of the more reactive, conformationally restricted cyclopentadiene **4b** at 130 °C led only to the conversion of reactant **1b** to pyridine **3b** (>90%). Decreasing the temperature to 110 °C caused a lower conversion, favoring the formation of a single adduct at the expense of undesired side product **3b**. Purification yielded compound **12d** in low yield, the result of a formal IED cyclization process (entry 8). Activation by either microwave radiation or pressure provided much better conversions and isolated yields (entries 9 and 10). In each case, a single and identical isomer was again produced. NOESY NMR experiments unambiguously indicated structure **12d** (Figure 3). Thus, through-space interactions could be demonstrated between H-10 and both H-3 and H-4, H-7 and H-5a, and H-6 and H-5b. The process was completely regioselective and apparently

(11) The transfer of the sulfonyl group from nitrogen to oxygen is probably disfavored under hyperbaric conditions. See ref 9 for various discussions on this type of process.

(12) Biactivation by Lewis acids and high pressures has been reported to induce higher yields and selectivities. See: (a) Revial, G.; Blanchard, M.; d'Angelo, J. *Tetrahedron Lett.* **1983**, *24*, 899−902. (b) Engler, T. A.; Naganathan, S.; Tagusakawa, F.; Yohannes, D. *Tetrahedron Lett.* **1987**, *28*, 5267−5270. (c) Sato, M.; Abe, Y.; Kaneko, C.; *J. Chem. Soc., Perkin Trans 1* **1990**, 1779−1783. (d) Minuti, L.; Scheeren, H. W.; Selvaggi, R.; Taticchi, A. *Synth. Commun.* **1992**, *22*, 2965−2969. (e) Posner, G. H.; Ishihara, Y. *Tetrahedron Lett.* **1994**, *35*, 7545−7548. (f) Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515−8538. (g) Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806−3814. (h) Posner, G. H.; Hutchings, R. H.; Woodward, B. T. *Synlett* **1997**, 432−434. (i) Chataigner, I.; Hess, E.; Toupet, L.; Piettre, S. R. *Org. Lett.* **2001**, *3*, 515−518. (j) Flessner, T.; Ludwig, V.; Siebeneicher, H.; Winterfeldt, E. *Synthesis* **2002**, 1373−1378. (k) Chrétien, A.; Chataigner, I.; Lhélias, N.; Piettre, S. R. *J. Org. Chem.* **2003**, *68*, 7990−8002.

(13) Interaction between the diene and the dienophile occurred exclusively from the less hindered, convex face of the latter; there are precedents in the literature for such behavior. See, for instance: (a) Grieco, P. A.; Lis, R.; Zelle, R. E.; Finn, J. *J. Am. Chem. Soc.* **1986**, *108*, 5908−5919. (b) Ashton, P. R.; Brown, G. R.; Isaacs, N. S.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Slawin, A. M. Z.; Smith, D. R.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 6330−6353. (c) Lautens, M.; Phillion, E. *J. Org. Chem.* **1996**, *61*, 7994−7995. (d) Lautens, M.; Phillion, E. *J. Org. Chem.* **1997**, *62*, 4418- 4427. (e) Deléens, R.; Gautier, A.; Piettre, S. R. *Tetrahedron Lett.* **2002**, *43*, 4963−4968.

TABLE 1. Reaction between 1-Tosylpyridone 1b and Dienes 4a−c under Thermal, Microwave, or Hyperbaric Activation

entry	diene[a]	method of activation[b]	reaction conditions	reaction time (h)	conv (%)[c]	NED DA adduct	yield (%)[d]	IED DA adduct	yield (%)[d]	bisadduct	yield (%)[d]	global yield (%)[d]
1	**4a**	A	*o*-xylene, 180 °C	48	100	**10a**	46[e]	−	−	−	−	46[f]
2	**4a**	A	toluene, $ZnCl_2$, 110 °C	120	83	**10a**	47[e]	−	−	−	−	47
3	**4a**	A	toluene, $ZnCl_2$, 140 °C	72	100	**10a**	50[e]	−	−	−	−	50
4	**4a**	B	toluene, 150 °C	2	54	**10a**	−	−	−	−	−	−
5	**4a**	C	THF, 16 kbar	24	100	**10a**	55	−	−	**14a**	29	84
6	**4a**	C	THF, 16 kbar, $ZnCl_2$	36	100	**10a**	50	−	−	**14a**	29	79
7	**4a**	C	THF, 16 kbar, EuFOD	36	93	**10a**	48	−	−	**14a**	30	78
8	**4b**	A	toluene, 110 °C	24	46	−	−	**12d**	7[e]	−	−	7
9	**4b**	B	THF, 130 °C	1	64	−	−	**12d**	60	−	−	60
10	**4b**	C	THF, 16 kbar	24	100	−	−	**12d**	80	−	−	80
11	**4c**	B	THF, 130 °C	1	4[g]	−	−	−	−	−	−	−
12	**4c**	C	THF, 16 kbar	24[h]	−[i]	−	−	**12g**	50	−	−	50
13	**4c**	C	CH_2Cl_2, 16 kbar	24[h]	75	−	−	**12g**	67	−	−	67

[a] 5 equiv of diene used. [b] A, thermal activation; B, microwaves activation; C, hyperbaric activation at room temperature, unless otherwise indicated. [c] Conversion. [d] Isolated yield. [e] Pyridine 3b was isolated as byproduct. [f] See ref 3. [g] Pyridine 3b was the only observed product. [h] Experiment carried out at 50 °C. [i] Undetermined because of competitive polymerization.

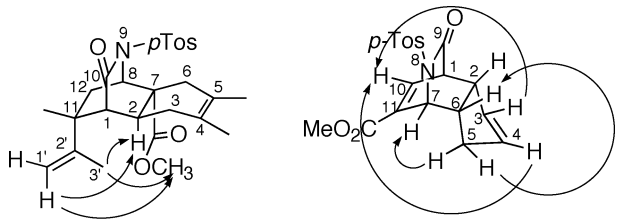


FIGURE 3. Representative selected NOE results for compounds **14a** and **12d**.

followed a completely *endo* stereoselective IED cycloaddition pathway.[14] Neither alternate cycloadducts **10d**, **11d,** and **13d** nor biscycloadducts **14d** and **15d** could be observed. The reaction with cyclohexadiene **4c** under microwave activation produced little conversion, and only side product **3b** could be observed by ^{1}H NMR spectroscopy (entry 11). However, when activated by a pressure of 16 kbar at room temperature (24 h), **4c** afforded IED cycloadduct **12g** (50% isolated yield) (entry 12). Similarly to cyclopentadiene **4b**, cyclohexadiene **4c** reacted in a completely regioselective and stereoselective fashion, with diastereomer **13g** apparently being disfavored under these conditions. Here again, neither cycloadducts **10g** and **11g**, resulting from an NED process, nor biscycloadducts **14g** and **15g** could be observed in the crude NMR spectra. Carrying out the reaction in methylene chloride somewhat improved the yield to 67% (entry 13).

Comparison of the data compiled in Table 1 indicates that high pressures (method C) constitute the most efficient method of activation. It is noteworthy that, in the case of diene **4a**, hyperbaric activation is the only technique leading to the formation of bisadducts **14a**. In addition, these conditions completely suppress the undesired transformation of pyridone **1b** into pyridine **3b** observed under either thermal or microwave activation.

To gain a more complete understanding of the behavior of **1b** in cross-cycloaddition reactions, we next studied its interaction, under hyperbaric conditions, with dienes bearing electron-donating group(s). Thus, 2-trimethylsilyloxycyclohexa-1,3-diene (**4d**), 2-trimethylsilyloxybuta-1,3-diene (**4e**), and 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (**4f**, Danishefsky's diene) were selected. Electron-rich 2-silyloxycyclohexadiene **4d** was more reactive than **4c**, producing complete conversion. Hydrolysis of the silyl enol ether moiety in the crude sample followed by chromatography gave NED cyclization compounds **16j** and **17j** (1:1 ratio of *endo* and *exo* diastereomers) in 35% isolated yield, as well as IED cycloadducts **12j** and **13j** (65%, 1:1 of *endo*/*exo* diastereomers) (Table 2, entry 1).[15] Whereas the regioselectivity of both NED and IED processes was absolute, no diastereoselectivity could be observed in either case. Interestingly, and in analogy to the behavior of unsubstituted cyclohexadiene **4c**, IED cycloadducts **12j** and **13j** did not further react to provide biscycloadducts **14j** and **15j**, presumably because of steric hindrance.

Under otherwise identical conditions, 2-silyloxybutadiene **4e** generated five products, isolated in 38% overall yield (entry 2). The major one, after hydrolysis of the silyl enol ether unit, proved to be NED cycloadduct **16m** (22% yield). In analogy

(14) *Endo* addition can be defined as "that particular spatial arrangement of reactants in which the more bulky side of the diene is under the more bulky side of the dienophile", meaning the pyridone cycle in this case. See: Fringuelli, F.; Taticchi, A. In *Dienes in the Diels-Alder Reaction*; John Wiley and Sons Ltd.: New York, 1990; pp 1−44.

(15) Hydrolysis of the silyl enol ethers was carried out by stirring a methylene chloride solution of the subtrate in the presence of silica; see Experimental Section.

TABLE 2. Reaction between 1-Tosylpyridone 1b and Dienes 4d−f under a Pressure of 16 kbar at Room Temperature

entry	diene[a]	reaction time (h)	conv (%)[b]	NED cycloadduct[c]	yield (%)[d]	IED cycloadduct	yield (%)[d]	biscycloadduct[c]	yield (%)[d]	global yield (%)[d]
1	**4d**	24	100	**16j**, **17j**	35[e]	**12j**, **13j**	65[e]	−	−	100
2	**4e**	24	78	**16m**	22	**12m**, **13m**	10[e]	**18m**, **19m**	6[e]	38
3	**4e**	54	100	**16m**	28	**12m**, **13m**	0	**18m**, **19m**	24[e]	52
4	**4f**[f]	54	100	**16p**, **17p**	61[g]	−	−	**19p**	13	74

[a] 5 equiv of diene used. [b] Conversion. [c] After hydrolysis of the silyl enol ether. [d] Isolated yields. [e] 1:1 mixture of endo and exo cycloadducts. [f] 2.5 equiv of diene used. [g] 55:45 mixture of *endo* and *exo* cycloadducts.

TABLE 3. Reaction between 1-Nosylpyridone 1c or 1-Triflylpyridone 1d and Dienes 4a−f under a Pressure of 16 kbar at Room Temperature after 24 h

entry	pyridone	diene	equiv of **4**	conv (%)[a]	NED cycloadduct	yield (%)[e]	IED cycloadduct	yield (%)[e]	biscycloadduct	yield (%)[e]	global yield (%)[e]
1	**1c**	**4a**	5	80	**10b**	52	**12b**	13	**14b**	14	79
2	**1c**	**4a**	5	100[b]	**10b**	74	−	−	**14b**	23	97
3	**1c**	**4b**	5	100	−	0	**12e**	71	−	−	71
4	**1c**	**4c**	5	53[c]	−	−	**12h**	42	−	−	42
5	**1c**	**4c**	5	82[b,c]	−	−	**12h**	70	−	−	70
6	**1c**	**4d**	5	100	**16k**, **17k**	24	**12k**, **13k**	40	−	−	64
7	**1c**	**4e**	5	88	**16n**	41	**12n**, **13n**	18	**18n**, **19n**	16	75
8	**1c**	**4f**	2.5	100	**16q**, **17q**	56	−	−	**19q**	32	88
9	**1c**	**4f**	2.5	100[b]	**16q**, **17q**	68	−	−	−	−	68
10	**1d**	**4a**	5	100	**10c**	35	−	−	−	−	35
11	**1d**	**4b**	5	100	−	−	**12f**	55	−	−	55
12	**1d**	**4c**	2.5	100[d]	−	−	**12i**	19	−	−	19
13	**1d**	**4e**	5	100[c]	**16o**	17	−	−	−	−	17
14	**1d**	**4f**	5	100	**16r**, **17r**	65	−	−	−	−	65

[a] Conversion. [b] Carried out in CH_2Cl_2. [c] Carried out at 50 °C. [d] Carried out under a pressure of 12 kbar. [e] Isolated yield.

with diene **4d**, IED products **12m** and **13m** were also obtained, as a 1:1 mixture of diastereomers. The next isolated compounds were biscycloadducts **18m** and **19m** (1:1 mixture of diastereomers). Increasing the reaction time led to some yield improvement in both **16m** and **18m**/**19m**, at the expense of IED cycloadducts **12m** and **13m** (entry 3).

Hyperbaric interaction between pyridone **1b** and electron-rich diene **4f** paralleled the reaction between **1b** and **4a** and gave high isolated yields, furnishing the desired NED cycloadducts as a 2:1 mixture of *endo* and *exo* diastereomers (**16p** and **17p**, respectively; 61% isolated yield after hydrolytic workup) (entry 4). In addition, only bisadduct **15p**, featuring the vinyl unit trans to the carbomethoxy group, was found to have formed, and after analogous hydrolysis, biscycloadduct **19p** could be isolated as a colorless, crystalline solid. Close inspection of the crude NMR spectra indicated the mixture to be devoid of either diastereomer **14p** or its hydrolyzed derivative **18p**. *This result contrasts markedly with that obtained from dimethylbutadiene **4a***. In that case, only the diastereomer with the vinyl and carbomethoxy groups *cis* to one another formed (*vide supra*). NED adducts **16p** and **17p** could also be obtained by conducting the transformation under thermal or microwave activation; the products were obtained in yields of 48% and 58%, respectively, as 1:1 (thermal) or 2:1 (microwave) mixtures of diastereomers. No IED cycloadducts (**12p**, **13p**) or biscycloadducts (**14p**, **15p**) were formed under these conditions. Lewis acid catalysis was ineffective here.

Recrystallization of both **16p** and **19p** from ethyl acetate/cyclohexane provided crystals of quality sufficient to be subjected to X-ray diffraction analysis. The Supporting Information includes computer-generated ORTEP graphics obtained from the diffraction spectra of the two compounds. Both the IED cycloaddition reaction leading to the intermediate monoadduct **13p** (unobserved) and the subsequent NED cyclization proceed with high regioselectivity and stereoselectivity.

High-pressure activation thus constitutes the best means of promoting the NED cycloaddition. However, an IED process also takes place with electron-poor pyridones, yielding either the IED cycloadduct or a biscycloadduct resulting from reaction of the IED adduct with another equivalent of electron-rich diene. Cyclopentadiene and cyclohexadiene, however, display anomalous behavior here, yielding exclusively IED cycloadducts with complete regio- and stereoselectivity. Replacement of the 1-tosyl group with either an *o*-nosyl group or a triflyl group was next examined to modify the electronic nature of the substrate and study its influence on the course of the cycloaddition process.

Methyl 1-[(2-Nitrophenyl)sulfonyl]-6-oxo-1,6-dihydropyridine-3-carboxylate (1c). Unexpectedly, when pyridone **1c** reacted with 2,3-dimethylbutadiene **4a** in THF (16 kbar), a lower conversion than in the case of pyridone **1b** was observed. The three possible types of products, i.e., NED cycloadduct **10b**, IED compound **12b**, and biscycloadduct **14b**, were isolated by chromatography (Table 3, entry 1). All structures were unambiguously assigned on the basis of 1-D and 2-D NMR spectrometry experiments, and in analogy to the reaction with pyridone **1b**, the crude material was shown to be devoid of compounds **13b** and **15b**. Conducting the transformation in methylene chloride induced a complete conversion that translated into increased isolated yields of **10b** (74%) and **14b** (23%); in this case, IED cycloadduct **12b** was neither isolated nor observed, because of its complete conversion into bisadduct **14b** (entry 2).

Cyclopentadiene once again reacted as a dienophile with complete regio- and stereoselectivity to afford IED cycloadduct **12e** in 71% isolated yield (entry 3). This latter behavior was paralleled by cyclohexadiene **4c**, which led exclusively to the formation of the analogous IED product **12h**, isolated in 42% yield, because of the lower reactivity of this diene (entry 4). This yield was improved to 70%, however, when the experiment was conducted in methylene chloride at 50 °C (entry 5).

With the conformationally restricted silyloxycyclohexadiene **4d**, four products were identified. Hydrolysis of the enol ether units converted diastereomeric NED cycloadducts **10k** and **11k** into ketones **16k** and **17k** (24%) and into IED compounds **12k** and **13k** (40%, entry 6). Comparing entry 6 in Table 3 with entry 1 in Table 2 demonstrates that, under these conditions, the IED process involving either pyridone **1b** or **1c** is favored with 3-silyloxycyclohexadiene **4d**. No stereoselectivity was observed in either NED or IED transformation between **1c** and **4d**.

When reacted with silyloxybutadiene **4e**, pyridone **1c** displayed an enhanced but similar behavior to **1b** with regard to the NED process, as illustrated by the 41% isolated yield of **16n**, after hydrolysis and purification by chromatography (entry 7). This pyridone was also more reactive as a diene, and chomatography also afforded both IED cycloadducts **12n** and **13n** (2:1 *endo*/*exo*) and biscycloadducts **18n** and **19n** (3:1 *endo*/*exo*).

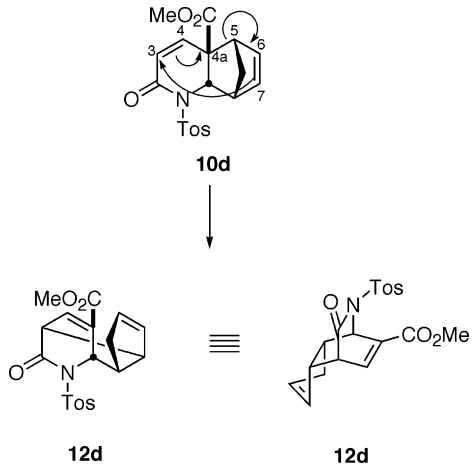
Comparison between entry 8 in Table 3 and entry 4 in Table 2 shows that the two pyridones **1b** and **1c** behave similarly with electron-rich diene **4f**, with **1c** affording NED Diels−Alder adducts **16q** and **17q** (7:3 *endo*/*exo*) and bisadduct **19q** in 56% and 32% isolated yields, respectively, after hydrolysis. The formation of IED adduct **13q** (which then further reacted with **4f**) is thus somewhat more favored from the nosylated reactant **1c**. Carrying out the reaction in methylene chloride reversed this trend and allowed the formation of **16q** and **17q** in 68% isolated yield without improving the stereoselectivity of the process (entry 9). No bisadduct **19q** was found to have formed under these reaction conditions.

Methyl 6-Oxo-[(1-trifluoromethyl)sulfonyl]-1,6-dihydropyridine-3-carboxylate (1d). Our recent findings on the enhanced dienophilicity of *N*-triflated electron-poor five-membered nitrogen heterocycles, when compared to the analogous *N*-tosylated reactant, induced us to check the behavior of 1-triflylpyridone **1d**.[16] However, the propensity of **1d** to transfer the sulfonyl group to the neighboring C2 oxygen atom, thus furnishing unreactive pyridine **3d**, was immediately noted. This behavior has a highly detrimental impact on the reactivity of **1d**, as lower yields and difficult purifications result therefrom. Results compiled in Table 3 (entries 10−14) confirm the behavior observed with pyridones **1b** and **1c**. Large amounts of pyridine **3d** were isolated each time, indicating the competitiveness of sulfonyl transfer with the pericyclic processes. The products were also found to readily decompose on silica, and low yields were obtained in several instances.

Discussion

Alkyl-Substituted Dienes 4a−c: Acyclic Dienes versus Cyclic Dienes. Analysis of the data in Tables 1 and 3 (entries 1−5 and 10−12) clearly shows a major difference in the behavior of alkyl-substituted dienes **4a−c**. Thus, whereas acyclic dimethylbutadiene (DMB) **4a** mainly reacts as a diene to achieve an NED Diels−Alder process and gives products **10a−c**, regardless of both the pyridone nitrogen substitution and the mode of activation, cyclopentadiene **4b** and cyclohexadiene **4c** exclusively behave as dienophiles to yield IED cycloadducts **12d−i**. The *s-cis* planar conformation of the conjugated moiety

SCHEME 2



in both **4b** and **4c** markedly differs from the calculated reactive conformation of acyclic diene **4a**, which has been shown to be *gauche*, deviating 38° from planarity, as a result of steric interaction between the two methyl groups.[17] Literature data unambiguously show that this conformational difference translates into a higher reactivity of **4b** and, to a lesser extent, of **4c**, as a diene in NED processes, *in stark contrast to the observed reactivity of **4b** and **4c** in the present study*.

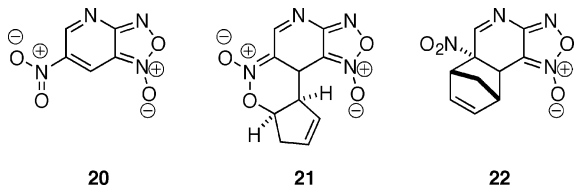
Alkyl-Substituted Dienes 4a−c: Involvement of a Cope Rearrangement? Actually, products **12d−i** might form either through a highly stereoselective IED process or *via* a sequence of reactions involving (i) an NED reaction, giving rise to unobserved products **10d−i**, and (ii) a stereospecific Cope rearrangement of **10d−i** involving the C3−C4 and C6−C7 carbon−carbon double bonds, as well as the C4a−C5 single bond, to generate the formal IED cycloadducts **12d−i** (Scheme 2). Indeed, the literature reports a few examples of such sequential processes yielding formal IED cycloadducts. Thus, Chou and Hung reported that sulfonyl dienes, when reacted at 130 °C with cyclopentadiene **4b**, give only IED cycloadducts.[4] However, when the reaction was carried out at room temperature, a mixture of NED cycloadducts and IED products was obtained. The former was completely stable at room temperature, but could be quantitatively transformed to the latter by heating at 130 °C, thereby demonstrating the partial involvment of the [3,3] sigmatropic rearrangement in the process. An analogous case was more recently reported for the reaction between cyclopentadiene **4b** and 6-substituted 1-nitrocyclohexadienes.[18] Here again, IED cycloadducts were unambiguously shown to arise through a Cope rearrangement of primary NED cycloadducts. To verify the possible participation of such a sequence in the reaction of pyridones **1** with dienes **4b** and **4c**, interaction between **1b** and cyclopentadiene **4b** was carried out at 25 and 50 °C; however, no change could be observed over extended periods of time (up to 7 days), indicating that substrate **1b** is less reactive as a dienophile than the above sulfonyl- or nitro-substituted dienes.[19]

(16) (a) Chataigner, I.; Chrétien, A.; Piettre, S. R. *Chem. Commun.* **2005**, 1351−1353. (b) Chrétien, A.; Chataigner, I.; Piettre, S. R. *Tetrahedron* **2005**, *61*, 7907−7915.

(17) (a) Squillacote, M. E.; Semple, T. C.; Mui, P. W. *J. Am. Chem. Soc.* **1985**, *107*, 6842−6846. (b) Bradley, A. Z.; Kociolek, M. G.; Johnson, R. P. *J. Org. Chem.* **2000**, *65*, 7134−7138. (c) Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* **2002**, *67*, 6823−6826.

(18) Román, E.; Baños, M.; Higes, F. J.; Serrano, J. A. *Tetrahedron: Asymmetry* **1998**, *9*, 449−458.

(19) Only dimerization of cyclopentadiene could be observed.



20 **21** **22**

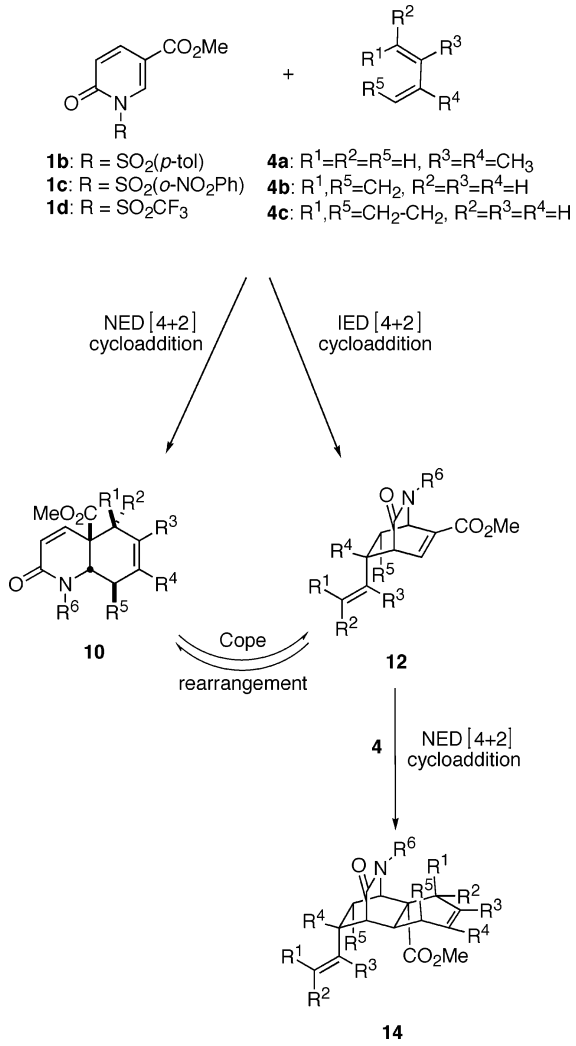
FIGURE 4. Structures of compounds **20**−**22**.

Acyclic Diene 4a under High Pressure: Isolation of Biscycloadducts 14. The results of hyperbaric and thermal activation differ in the case of DMB **4a**. Under high pressures, bisadducts **14a** (Table 1, entries 5−7) and **14b** (Table 3, entry 2) were isolated in yields ranging from 23% to 30%. The formation of these products can be rationalized through the intermediacy of IED monoadducts **12a** and **12b**. Indeed, hyperbaric conditions under which conversion was incomplete allowed the isolation of IED product **12b** (Table 3, entry 1). Each one of these products displayed data in accordance with complete regio- and stereochemistries similar to those observed in IED products isolated from dienes **4b** and **4c**. Spino et al.'s analysis of literature data on cross-Diels−Alder reactions clearly indicates that electron-poor dienes almost invariably behave as dienophile when reacted with electron-rich dienes, thus generating NED cycloadducts.[20] According to this analysis, interaction between pyridones **1b**−**d** and cyclic dienes **4b** and **4c** should yield the unobserved NED adducts **10d**−**i** (as well as **11d**−**i** in case of incomplete stereoselectivities).

However, Chou and Hung's conclusion on the behavior of sulfonyl dienes, when reacted with cyclopentadiene, favors the involvement of *both* routes. Other literature data indicate that IED Diels−Alder process might be kinetically favored over NED cycloadditions. Dominguo et al. reported one such example, in which a nitroarene substrate **20** reacts at −20 °C as the 4π-electron component with cyclopentadiene (acting as a dienophile) to generate product **21**, the result of an IED [4 + 2] heterocycloaddition (Figure 4).[21,22]

However, upon heating at 0 °C, this kinetic product underwent a [3,3] sigmatropic rearrangement to furnish the thermodynamic NED [4 + 2] adduct **22**. This type of behavior has been supported by theoretical studies.[23] These data clearly show that, at least in some cases, the IED process can compete with the corresponding NED reaction. Actually, three possible pathways exist to account for the observed products, depending on which primary product is formed (Scheme 3): (i) the NED product **10** is the only primary formed compound and is partly converted by a Cope rearrangement into **12**, which is thereafter transformed into biscycloadduct **14** through a subsequent reaction with DMB; (ii) the IED cycloadduct is the exclusive primary product and is competitively transformed into both NED cycloadduct **10** (Cope rearrangement) and biscycloadduct **14**; and (iii) both NED and IED monocycloadducts **10** and **12** are formed in parallel, the latter being subsequently transformed into **14**. This latter

SCHEME 3



possibility does not rule out involvment of the Cope rearrangement in either direction (NED → IED or IED → NED). In our case, compression of NED monoadduct **10a** to 16 kbar in the presence of 5 equiv of DMB **4a** failed to generate bisadduct **14a**. This result shows that, as expected, the NED retrocycloaddition is disfavored under the reaction conditions. In addition, this suggests that IED cycloadduct **12a** is not the result of a Cope rearrangement of **10a**, which rules out the first pathway. Heating NED cycloadduct **10a** at 250 °C for 3 days did not further induce the formation of IED product **12a**, with the substrate recovered unchanged.

Alkyl-Substituted Dienes 4a−c under High Pressure: Is an IED → NED Cope Rearrangement Involved? The Cope rearrangement is known to be reversible and to strongly depend on both the substitution and the conformation of substrate and product. Cases of both NED → IED (usually favored) and IED → NED rearrangements have been reported (see above).[24] The lack of any Cope rearrangement from NED cycloadduct **10a** to IED product **12a** led us to verify the possible involvement of an analogous, reverse sigmatropic process (i.e., IED → NED). Thus, when IED nosylated cycloadduct **12b** was heated at 220 °C for 36 h, a clean transformation occurred, quantitatively

(20) (a) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int Ed.* **1998**, *37*, 3262−3265. (b) Spino, C.; Rezaei, H.; Dory, Y. L. *J. Org. Chem.* **2004**, *69*, 757−764.

(21) Arroyo, P.; Picher, M. T.; Dominguo, L. R.; Terrier, F. *Tetrahedron* **2005**, *61*, 7359−7365.

(22) Nitroalkenes, when reacted with dienes under $SnCl_4$ catalysis, have been shown to yield inverse-electron-demand [4 + 2] heterocycloadducts, rather than normal-electron-demand [4 + 2] products. See: Denmark, S. E.; Kesley, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912−4924.

(23) Yamabe, S.; Dai, T.; Minato, T. *J. Am. Chem. Soc.* **1996**, *118*, 10994−10997.

(24) Hill, R. K. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; pp 785−826.

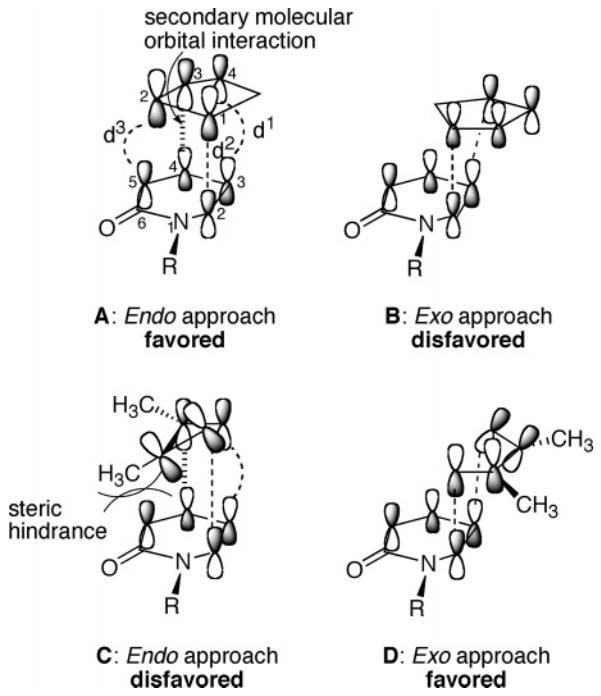


FIGURE 5. *Endo* and *exo* approaches between cyclopentadiene **4b** and 2-pyridones **1** and between dimethylbutadiene **4a** and 2-pyridones **1** (ester group deleted for clarity).

yielding NED product **10b**. The possibility of **10b** arising from a sequence of reactions involving (i) an IED retrocycloaddition and (ii) an NED Diels−Alder process can reasonably be eliminated in view of both the high yield of the transformation and the absence of any trace of pyridine **3c**, a compound whose formation was shown to be favored under thermal conditions (*vide supra*). This result does indicate the viability of a thermal Cope rearrangement from IED adducts to NED products. High-pressure activation (16 kbar, 25 °C, 24 h), however, did not promote this **12b** → **10b** sigmatropic rearrangement, the substrate being recovered unchanged. These results also clearly indicate that NED adduct **10b** is the thermodynamic product and suggest that, under hyperbaric activation, both routes are competitive, thus simultaneously providing **10b** and **12b**. Attempts to carry out the Cope rearrangement at 250 °C on the IED cycloadduct **12e** [the exclusive product from the reaction between nosylpyridone **1c** and cyclopentadiene **4b** (Table 3, entry 3)] mainly resulted in a retrocycloaddition process, as evidenced by the isolation of *O*-nosylpyridine **3c** in 50% yield. Another, unidentified product, devoid of any nosyl group, was also isolated in low yield (<20%). These data would indicate that the IED cycloadducts generated from the conformationally restricted *s*-cis dienes **4b** and **4c** are the thermodynamic products.[25]

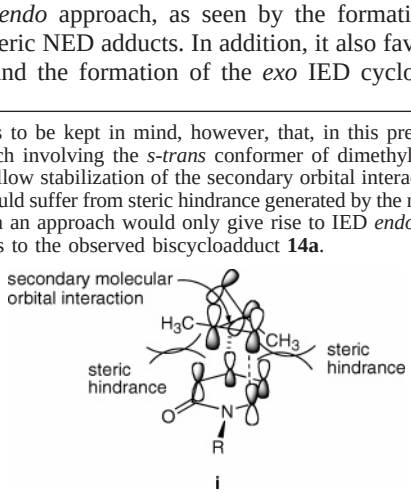
Alkyl-Substituted Dienes 4a−c under High Pressure: *Endo* and *Exo* Approaches. Close inspection of both *endo* and *exo* approaches (A and B, respectively) shows that, as expected, the former approach allows for the development of stabilizing secondary orbital interactions (Figure 5). An asynchronous, concerted mechanism would probably favor the formation of a σ bond between carbon 2 of substrate **1** and carbon 1 of cyclopentadiene **4b** more than that between either carbon 3 of **1** and carbon 4 of cyclopentadiene (NED process) or carbon 5 of **1** and carbon 2 of cyclopentadiene (IED process). Inasmuch as both NED and IED reactions involve the same frontier molecular orbitals (i.e., LUMO of pyridone and HOMO of cyclopentadiene), the outcome of the interaction depends on the extent of orbital overlap between either positions 3 of substrate **1** and 4 of diene **4b** (d^1 small) or positions 5 of **1** and 2 of diene **4b** (d^3 small). The slightly twisted positioning of cyclopentadiene over **1** in the favored *endo* approach (the result of steric hindrance generated by the methylene unit in **4b**) suggests the development of a second σ bond between carbons 5 of **1** and 2 of **4b**, rather than between carbons 3 of **1** and 4 of **4b**, to generate IED cycloadducts **12**.

An analogous argument can be made with cyclohexadiene **4c**. In the case of dimethylbutadiene **4a**, the *gauche* conformation would induce a larger steric hindrance from the methyl groups in C and would favor an *exo* approach D, thus leading to an NED process.[26] It is also of interest to note that the ester group on carbon 3 of substrates **1** will stabilize the strong double-bond character between C3 and C4 in the transition state leading to IED adducts **12** and **13**.[27] In addition, a more pronounced asynchronicity has been reported to give rise to a more stable transition state in IED Diels−Alder processes.[21a]

Silyloxy-Substituted Dienes 4d−f. The presence of a silyloxy group in dienes **4d−f** generated both NED cycloadducts **10** and **11** (**16** and **17** after hydrolysis of the silyl enol ether group) and IED cycloadducts **12** and **13**, the latter being partly or completely transformed into biscycloadducts **14** and/or **15** and isolated in the form of compounds **18** and/or **19**, respectively, after hydrolysis (Table 2, entries 1−4, and Table 3, entries 6−9 and 13−14). Although regiochemistry in both NED and IED monocycloadducts proved to be complete in every case, the stereoselectivity was not, with dienes **4d** and **4e** invariably generating mixtures of the two possible diastereomers. The presence of the silyloxy substituent on cyclohexadiene alters its reactivity by inducing the formation of both NED and IED cycloadducts (compare entry 1 in Table 2 with entry 12 in Table 1, as well as entries 4−6 in Table 3). The threefold effect resulting from the steric hindrance generated by this group not only renders the *exo* approach competitive with the endo approach, but also somewhat disfavors the formation of the σ bond between carbon 5 of pyridones **1** and carbon 2 of diene **4d** in the *endo* approach, as seen by the formation of both diastereomeric NED adducts. In addition, it also favors the *exo* approach and the formation of the *exo* IED cycloadduct **13**.

(25) Molecular model inspection shows that the two double bonds in **12d−f** are closer than those in **12a−c**. Hence, the [3,3] sigmatropic rearrangement should be more favored from the IED cycloadducts obtained from cyclopentadiene, if the equilibrium is shifted towards the formation of the NED adducts.

(26) It has to be kept in mind, however, that, in this precise case, an *endo* approach involving the *s-trans* conformer of dimethylbutadiene **4a** would also allow stabilization of the secondary orbital interactions to take place, but would suffer from steric hindrance generated by the methyl groups as well. Such an approach would only give rise to IED *endo* cycloadduct **12a**, and thus to the observed biscycloadduct **14a**.



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(27) Spino, C.; Crawford, J.; Cui, Y.; Gugelchuk, M. *Perkin Trans 2* **1998**, 1499−1506.

Interestingly, in the case of Danishefsky's diene **4f**, compounds **19p** and **19q** (Table 2, entry 4, and Table 3, entry 8) were the exclusive hydrolyzed biscycloadducts, and not a trace of the diastereomeric adducts **18** (or unhydrolyzed **14**) was observed. In the precise case of biscycloadducts **19p** and **19q**, the *cis* relationship between the amide carbonyl unit and the methoxyvinyl group obviously removes any possibility of a Cope rearrangement of primary NED cycloadduct **10p**. This absence of any diastereomeric adduct **18** might reflect a completely *exo* stereoselective IED process to provide **13p** from **1b**, or **13q** from **1c**, but not **12p** or **12q**. In the alternative case of a partially, or non-, stereoselective IED reaction, the *endo* IED diastereomer could undergo a fast Cope rearrangement to **10p** (or **10q**), thus preventing it from reacting with another equivalent of diene to yield biscycloadduct **14p** (or **14q**). It is well to bear in mind, however, that [3,3] sigmatropic rearrangements are characterized by a much smaller volume of activation ($\Delta V^{\neq} \approx -10$ mL/mol) than the [4 + 2] processes ($\Delta V^{\neq} \approx -40$ mL/mol).[28] This fact speaks in favor of a stereoselective IED reaction in this case. The reasons behind this complete reversal of stereoselectivity, when compared to dimethylbutadiene **4a**, remain unclear.

The somewhat different behavior of silyloxy-substituted dienes can also be related to either more polarized transition states or even an alternate, stepwise mechanism.[29] Cycloaddition reactions with Danishefsky's diene, in particular, might proceed *via* a Mukaiyama-like type of mechanism, involving a Michael addition of the electron-rich silyl enol ether species on the dienophile, followed by a second cyclization step.[30] It is interesting to note, however, that pyridone **1b** failed to react with either *n*-butyl vinyl ether or 4,5-dihydrofuran, when placed under otherwise identical conditions. In any case, no trans-fused NED cycloadducts analogous to **10** or **11** were ever observed in this study.

Conclusion

6-Oxo-1,6-dihydropyridine-3-carboxylates bearing a sulfonyl unit in position 1 react under thermal, microwave, or hyperbaric activation with electron-rich dienes to afford either normal-electron-demand (NED) cycloadducts and/or inverse-electron-demand (IED) products, depending on the diene. Thus, cyclic dienes, such as cyclopentadiene **4b**, cyclohexadiene **4c**, and silyloxycyclohexadiene **4d** clearly favor the IED process, whereas acyclic dienes **4a**, **4e**, and **4f** furnish only (thermal or microwave activation) or mainly (hyperbaric activation) the NED products. When activated by high pressures, IED primary products generated from acyclic dienes most often react with a second equivalent of diene to give biscycloadducts **14** or **15**. In addition, hyperbaric activation completely suppresses the undesired, competitive transformation of the substrates into the corresponding, unreactive pyridines.

Analysis of the data indicates that, under hyperbaric activation, NED and IED processes are competitive. Although evidence consistent with a Cope rearrangement could be obtained under thermal conditions (**12b** → **10b**), hyperbaric conditions failed to yield the same result. In a similar way, no transformation of NED compounds into IED products could be achieved under high pressure. These and other data establish the cross-cycloaddition nature of the processes described in this work. Steric hindrance and conformational behavior are suggested to play a role in and account for the competition between the NED process and the IED cycloaddition reaction. Additional experimental and theoretical works are in progress to shed light on the differences in reactivity and stereoselectivity observed in the above reactions.

Experimental Section

General. ^{1}H NMR (300 MHz), ^{19}F NMR (282 MHz), and ^{13}C NMR (75 MHz) spectra were recorded in deuterated chloroform relative to $(CH_3)_4Si$, $FCCl_3$, and $CDCl_3$, respectively. Chemical shifts are expressed in parts per million (ppm), and couplings in Hertz. Low- and high-resolution mass spectra were recorded under either EI, CI, or FAB conditions, operating in positive ion mode. IR spectra were recorded as films or as pellets. Hyperbaric experiments were conducted on a Unipress U101 or Psika Pressure Systems Ltd. apparatus. Microwave experiments were conducted in a Discover reactor manufactured by CEM Corporation; the temperatures were measured using an IR probe. Nitrogen gas was used as an inert atmosphere.

Pyridones 1 and Methyl 6-hydroxypyridine-3-carboxylate. Methyl 6-hydroxypyridine-3-carboxylate[31] and methyl 1-(4-methylbenzenesulfonyl)-6-oxo-1,6-dihydropyridine-3-carboxylate **1b**[3] were prepared according to the literature procedures.

Representative Procedure for Cycloaddition Reactions under High-Pressure Activation. To a stirring solution of pyridone **1b** (1.84 g, 6 mmol) in dry THF (15 mL) was added freshly distilled dimethylbutadiene (2.85 mL, 25 mmol). The resultant solution was placed into a 20-mL high-pressure vessel, compressed at 16 kbar, and maintained at this pressure for 24 h. After decompression, the solvent and excess diene were evaporated under reduced pressure. The residue was purified by flash chromatography on silica (cyclohexane/ethyl acetate 5:1 followed by 4:1) to sequentially yield pure **14a** (0.82 g, 1.74 mmol; 29%) and pure **10a** (1.09 g, 2.8 mmol). The following fraction was concentrated to give an oily material (0.33 g) that was crystallized by addition of diethyl ether. Filtration afforded another 0.19 g (0.5 mmol) of pure **10a**[3] (1.28 g total, 3.3 mmol; 55%).

Methyl 9-Aza-4,5,11-trimethyl-9-[(4-methylphenyl)sulfonyl]-11-(1-methylethenyl)-10-oxo-tricyclo[$6^{1.8}.2^{1.8}.2^{1.8}.0^{2.7}$]dodec-4-ene-7-carboxylate (14a). Colorless solid (mp 95−97 °C). ^{1}H NMR δ 0.57 (s, 3H), 1.46 (dd, 1H, J = 14.5, 4.2 Hz), 1.62 (s, 3H), 1.65 (s, 3H), 1.66 (s, 3H), 1.76 (dd, 1H, J = 14.7, 9.3 Hz), 2.03 (dd, 1H, J = 14.5, 1.5 Hz), 2.07 (dd, 1H, J = 14.7, 6.5 Hz), 2.26 (m ≈ bs, 2H), 2.37 (d, 1H, J = 1.8 Hz), 2.43 (s, 3H), 2.76 (ddd, 1H, J = 9.3, 6.5, 1.8 Hz), 3.70 (s, 3H), 4.66 (m ≈ bs, 1H), 4.89 (m ≈ bs, 1H), 4.90 (dd, 1H, J = 4.2, 1.5 Hz), 7.33 (d, 2H, J = 8.3 Hz), 7.96 (d, 2H, J = 8.3 Hz). ^{13}C NMR δ 18.76, 18.79, 20.0, 21.7, 29.1, 33.7, 34.9, 35.3, 37.7, 41.3, 52.4, 52.6, 54.8, 59.4, 111.8, 125.1, 126.9, 128.4 (2C), 129.4 (2C), 135.7, 145.0, 148.0, 171.8, 174.8. IR (KBr) ν 2951, 2926, 2855, 1732, 1719, 1454, 1355, 1239, 1170, 1089, 875, 720, 670 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 471 (80) [M$^+$], 316 (22), 284 (63), 152 (100), 91 (38). Anal. Calcd for $C_{26}H_{33}NO_5S$: C, 66.22; H, 7.05; N, 2.97; S, 6.80. Found: C, 66.67; H, 7.35; N, 3.03; S, 6.54.

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In the case of Danishefsky's diene **4f** (95 μL, 0.5 mmol) and pyridone **1b** (62 mg, 0.2 mmol), the purification was as follows: After decompression, the solvent was evaporated under reduced pressure, and the excess diene was eliminated by bulb-to-bulb distillation under reduced pressure (50 °C/0.1 bar). The residue was then stirred overnight in methanol (2 mL) in the presence of silica (100 mg) to hydrolyze the silyl enol ether moiety. After filtration on celite and concentration under reduced pressure, the oily material was purified by flash chromatography on silica (cyclohexane/ethyl acetate 2:1 followed by 1:1) to sequentially give **16p** (34 mg, 42%), **17p** (15 mg, 19%), and **19p** (15 mg, 13%).

(4a*R,5*R**,8a*S**)-Methyl 5-Methoxy-2,7-dioxo-1-[(4-methylphenyl)sulfonyl]-1,2,4a,5,6,7,8,8a-octahydroquinoline-4a-carboxylate (16p).** Colorless solid (mp 199−201 °C). ^{1}H NMR δ 2.24−2.33 (m, 1H), 2.41 (s, 3H), 2.60 (dd, 1H, J = 15.1, 12.1 Hz), 2.84−2.93 (m, 2H), 3.35 (s, 3H), 3.65 (s, 3H), 3.98 (dd, 1H, J = 12.1, 4.3 Hz), 5.22 (ddd, 1H, J = 11.7, 5.7, 1.9 Hz), 6.18 (d, 1H, J = 9.8 Hz), 6.96 (dd, 1H, J = 9.8, 1.9 Hz), 7.30 (d, 2H, J = 8.3 Hz), 7.87 (d, 2H, J = 8.3 Hz). ^{13}C NMR δ 21.6, 42.4, 44.5, 53.6, 54.6, 55.8, 57.7, 78.3, 127.6, 129.0 (2C), 129.3 (2C), 135.5, 139.5, 145.3, 160.6, 171.5, 201.6. IR (KBr) ν 3058, 2952, 2840, 1731, 1695, 1597, 1434, 1381, 1353, 1242, 1169, 1094, 1029, 984, 917, 822, 735, 663 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 343 (85), 311 (65), 244 (100), 91 (95). Anal. Calcd for $C_{19}H_{21}NO_7S$: C, 56.01; H, 5.20; N, 3.44; S, 7.87. Found: C, 56.05; H, 5.34; N, 3.48; S, 7.78.

(4a*R,5*S**,8a*S**)-Methyl 5-Methoxy-2,7-dioxo-1-[(4-methylphenyl)sulfonyl]-1,2,4a,5,6,7,8,8a-octahydroquinoline-4a-carboxylate (17p).** Colorless solid (mp 214−216 °C). ^{1}H NMR δ 2.42 (s, 3H), 2.35−2.50 (m, 1H), 2.55 (dd, 1H, J = 14.7, 11.3 Hz), 2.84 (ddd, 1H, J = 15.0, 3.8, 2.3 Hz), 3.05 (ddd, 1H, J = 14.7, 6.4, 2.3 Hz), 3.33 (s, 3H), 3.74 (s. 3H), 4.25 (dd, 1H, J = 3.8, 2.3 Hz), 5.75 (ddd, 1H, J = 11.3, 6.4, 1.9 Hz), 6.05 (d, 1H, J = 9.8 Hz), 6.53 (dd, 1H, J = 9.8, 1.9 Hz), 7.31 (d, 2H, 8.3), 8.04 (d, 2H, J = 8.3 Hz). ^{13}C NMR δ 21.6, 39.6, 44.6, 52.3, 53.0, 54.1, 56.9, 81.2, 126.7, 129.0 (2C), 129.5 (2C), 135.6, 139.6, 145.3, 160.1, 168.8, 202.3. IR (KBr) ν 3058, 2963, 2931, 1732, 1687, 1389, 1345, 1258, 1238, 1168, 1088, 907, 732 cm^{-1}. MS (CI, C_4H_{10}) *m*/*z* (relative intensity) 408 (100) [M + H]$^+$. HRMS. Calcd for $C_{19}H_{22}NO_7S$: (MH^+) 408.1117. Found: 408.1108.

Methyl 9-Aza-6-methoxy-11-[(*E*)-2-methoxyvinyl]-11-trimethylsilyloxy-9-[(4-methylphenyl)sulfonyl]-4,10-dioxo-tricyclo-[6$^{1.8}$.2$^{1.8}$.2$^{1.8}$.0$^{2.7}$]dodecane-7-carboxylate (19p). Colorless solid (mp 180 °C). ^{1}H NMR δ 0.00 (s, 9H), 1.96 (dd, 1H, J = 15.1, 3.8 Hz), 2.14−2.43 (m, 5H), 2.44 (s, 3H), 2.95 (dd, 1H, J = 18.8, 6.0 Hz), 3.20 (s, 3H), 3.26 (ddd, 1H, J = 13.6, 6.0, 2.6 Hz), 3.46 (s, 3H), 3.74 (s, 3H), 4.05 (dd, 1H, J = 11.7, 6.0 Hz), 4.43 (d, 1H, J = 13.2 Hz), 5.29 (dd, 1H, J = 3.8, 2.3 Hz), 5.81 (d, 1H, J = 13.2 Hz), 7.32 (d, 2H, J = 8.2 Hz), 7.92 (d, 2H, J = 8.2 Hz). ^{13}C NMR δ 2.1 (3C), 21.6, 31.2, 40.0, 40.4, 42.1, 52.4, 53.1, 53.8, 55.6, 57.4, 59.5, 72.2, 75.5, 108.4, 128.3 (2C), 129.4 (2C), 135.3, 145.4, 149.0, 169.4, 171.4, 206.5. IR (KBr) ν 2956, 2837, 1723, 1648, 1435, 1354, 1259, 1212, 1170, 1101, 1075, 1049, 982, 842, 718, 672 cm^{-1}. MS (EI) *m*/*z* (relative intensity) 579 (88) [M]$^+$, 564 (100), 548 (7), 424 (32), 392 (20), 91 (72). Anal. Calcd for $C_{27}H_{37}NO_9SSi$: C, 55.94; H, 6.43; N, 2.42; S, 5.53. Found: C, 55.74; H, 6.59; N, 2.41; S, 5.31.

Representative Procedure for Cycloadditions under Lewis Acid Activation. To a stirring solution of pyridone **1b** (307 mg, 1 mmol) in dry toluene (3 mL) placed in a pressure tube was added a 1 M solution of diethylzinc in diethyl ether (100 μL, 0.1 mmol) under inert atmosphere. The mixture was stirred for 1 h at room temperature, and freshly distilled dimethylbutadiene (564 μL, 5 mmol) was added. The resultant solution was heated at 140 °C for 72 h. After evaporation of the volatiles, the residue was purified by flash chromatography on silica (cyclohexane/ethyl acetate 5:1) to yield **10a** (194 mg, 50%).[3]

Representative Procedures for cycloaddition Reactions under Microwave Activation. To a stirring solution of pyridone **1b** (154 mg, 0.5 mmol) in dry THF (1 mL) was added freshly distilled cyclopentadiene (206 μL, 2.5 mmol). The solution was submitted to microwave irradiation in a sealed tube at 130 °C for 1 h. The resultant mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica (cyclohexane/ethyl acetate 2:1) to give **12d** (111 mg, 60%).

Methyl 8-Aza-9-[(4-methylphenyl)sulfonyl]-9-oxo-tricyclo-[5$^{1.7}$.2$^{1.7}$.2$^{1.7}$.0$^{2.6}$]undec-3,10-diene-11-carboxylate (12d). Colorless solid (mp 160 °C). ^{1}H NMR δ 1.82 (m, 1H), 2.40 (s, 3H), 2.42 (m, 1H), 3.13 (m, 1H), 3.35 (m, 1H), 3.59 (dd, 1H, J = 6.4, 2.6 Hz), 3.80 (s, 3H), 5.40 (m, 1H), 5.58 (m, 1H), 5.84 (m, 1H), 7.02 (dd, 1H, J = 6.4, 2.3 Hz), 7.27 (d, 2H, J = 8.3 Hz), 7.82 (d, 2H, J = 8.3 Hz). ^{13}C NMR δ 21.6, 35.3, 42.0, 48.1, 50.4, 52.3, 56.5, 127.9 (2C), 129.0, 129.5 (2C), 133.5, 134.4, 135.5, 141.3, 145.1, 163.5, 169.6. IR (KBr) ν 3098, 3053, 2947, 2921, 2860, 1717, 1542, 1438, 1368, 1287, 1264, 1236, 1181, 1089, 1021, 918, 731 cm^{-1}. MS (CI, C_4H_{10}) *m*/*z* (relative intensity) 374 (100) [M + H]$^+$, 273 (75). HRMS. Calcd for $C_{19}H_{20}NO_5S$: (MH^+) 374.1062. Found: 374.1075.

The same compound was also obtained under high-pressure activation, following the above representative procedure. The residue was purified by flash chromatography on silica (CH_2Cl_2/ethyl acetate 99.5/0.5) to yield **12d** (60 mg, 80%).

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Supporting Information Available: Procedures for compounds **1c** and **1d**, as well as for the thermal Cope rearrangement of **12b** into **10b**; analytical data for compounds **1c**,**d**, **3c**,**d**, **10b**,**c**, **12b**, **12e−i**, **12k−n**, **13j**,**k**, **13m**,**n**, **14a**,**b**, **16j**,**k**, **16n−r**, **17j**,**k**, **17m**, **17p−r**, **18n**, and **19n−q**, as well as ^{1}H NMR and ^{13}C NMR spectra of compounds **1b−d**, **3b**, **10a**, **10c**, **12d**, **12f−i**, **12k**, **12m**,**n**, **13k**, **13m**,**n**, **16n**, **16r**, **17p**, **17r**, and **19m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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