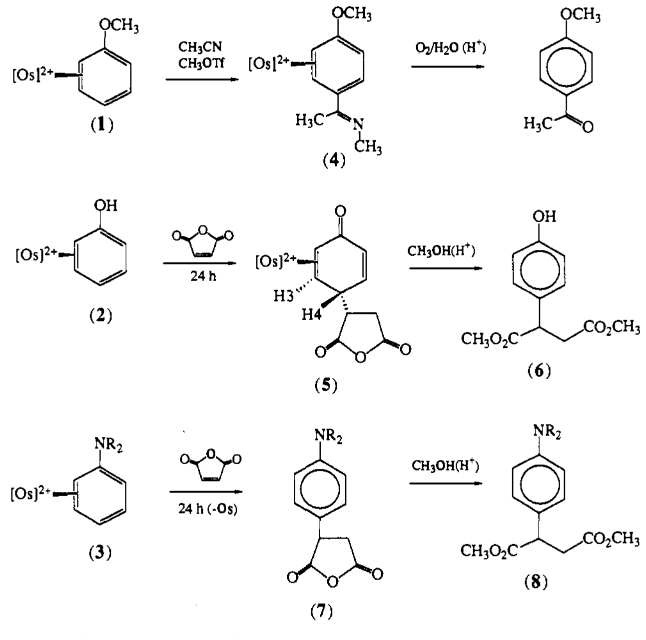
J. Am. Chem. Soc. **1991**, *113*, 8973-8975

Scheme I. Summary of Electrophilic Substitutions Promoted by Pentaammineosmium(II)^a



^{a} [Os]$^{2+}$ = [Os(NH$_3$)$_5$]$^{2+}$. R = CH$_3$, H. All reactions carried out at 20 °C in acetonitrile.

When N-substituted maleimides are substituted for maleic anhydride, the isolated yield of the succinyl product ranges from 60 to 80%.[18]

The aniline complex [Os(NH$_3$)$_5$[(2,3-η)-*N*,*N*-dimethylaniline]](OTf)$_2$ (69.5 mg, 0.1 mmol) (**3**) and maleic anhydride (9.8 mg, 0.1 mmol) were combined in CD$_3$CN (0.5 mL), and the resulting solution was monitored by ^{1}H NMR spectroscopy. After 15 min, a ^{1}H NMR spectrum indicated a mixture of products, but a pattern of four doublets ranging from 5.5 to 6.4 ppm suggested that one of these species was an η^2-bound para-disubstituted arene, similar to the products **4** and **5**. Over the next day these peaks diminished, yielding an organic material, **7**, whose ^{1}H and ^{13}C NMR and infrared data are consistent with [4-(dimethylamino)phenyl]succinic anhydride.[19] Treatment of the reaction mixture with acidic methanol resulted in the diester derivative **8** in 50% overall yield from **3** (Scheme I).[20]

The conjugate addition of maleic anhydride to phenol or *N*,*N*-dimethylaniline is unprecedented even in the presence of a Lewis acid, where the dominant reaction is an acylation.[21] Even when the aniline derivative of **3** is employed, conjugate addition to the ring is competitive with N-acylation, resulting in a 30% isolated yield of the corresponding diester. A full investigation of electrophilic additions and substitutions on η^2-arene complexes and the optimization of resulting organic products is currently in progress.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (PRF 23361-G), the University of Virginia, the Jeffress Memorial Trust (J-206), and Catalytica (Mountain View, CA) for their generous support of this work.

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[18] Treatment of **2** with 1 equiv of *N*-phenylmaleimide followed by oxidation results in >80% of (4-hydroxyphenyl)-*N*-phenylsuccinimide (yield not optimized).

[19] Characterization of **7**: ^{1}H NMR (CDCl$_3$) δ 7.10 (d, 2 H. CH), 6.71 (d, 2 H, CH), 4.23 (dd, 1 H, CH), 3.4 (dd, 1 H, CH$_2$), 3.1 (dd, 1 H, CH$_2$), 2.96 (s, 6 H, CH$_3$); ^{13}C NMR δ 173, 170, 151, 128, 122, 113, 46, 41, 37; IR (CD$_3$CN) 1861, 1788 cm^{-1}.

[20] Characterization of **8**: ^{1}H NMR (CDCl$_3$) δ 7.13 (d, 2 H, CH), 6.67 (d, 2 H, CH), 3.99 (dd, 1 H, CH), 3.663 (s, 3 H, CH$_3$O), 3.660 (s, 3 H, CH$_3$O), 3.15 (dd, 1 H, CH$_2$), 2.93 (s, 6 H. NCH$_3$), 2.63 (dd, 1 H, CH$_2$); ^{13}C NMR 174.4, 172.7, 150.4, 125.6, 113.1, 52.6, 52.2, 46.5, 40.9, 38.2; M$^+$ = 265; mp = 73–74 °C. Anal. (C$_{14}$H$_{19}$NO$_4$) C, H, N; C: calcd 63.38; found, 62.84.

[21] Koga, W. *Nippon Kagaku Zasshi* **1956**, *77*, 1276. Webster, V. S.; Kamstra, L. D. *Proc. S.D. Acad. Sci.* **1951**, *30*, 40.

Geometrical Aspects of the Activation of Enones by Titanium Tetrachloride: Diels–Alder Reactions

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A critical element in the rational design of chiral Lewis acids for effecting stereoselective cycloaddition reactions to achiral enones is an understanding of the geometry of the reactive enone–Lewis acid complex.[1,2] Experimental[3,4] and theoretical[5] studies indicate that an in-plane coordination geometry to carbonyls is thermodynamically preferred for the Lewis acids commonly employed by organic chemists. However, the thermodynamically favored geometry of a molecule or complex is not necessarily the same as the reactive geometry (cf. the Curtin–Hammett principle[6]).

To investigate the nature of the *reactive* geometry of enone–Lewis acid complexes in Diels–Alder reactions, we have examined the relative rate of reaction of cyclopentadiene with TiCl$_4$ complexes of diastereomeric 1-(methoxymethyl)-1-propylhexahydronaphthalen-2-ones **1a** and **1e**. Methoxymethyl groups in **1a** and **1e** are oriented to direct complexation to the π-system and to the plane of the carbonyl, respectively.[7] *n*-Propyl groups are included to minimize conformational differences between the compounds.

Molecular models[8] of **1a**·TiCl$_4$ indicate that while π-coordination of a chelated titanium is geometrically reasonable, in-plane complexation to a *planar* enone is unlikely. In **1e**·TiCl$_4$, complexation could occur either in the plane of the carbonyl or in the π-system on the α-face; however, in the latter position it would block any Diels–Alder reaction from the α-face. TiCl$_4$ seemed to be an apt choice for the activating Lewis acid; while a number

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[1] Examples and leading references for Diels–Alder reactions employing chiral Lewis acids: (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (b) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935. (c) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 4647. (d) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545. (e) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (f) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. (g) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1989**, *111*, 789. (h) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231. (i) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436.

[2] General references to Lewis acid mediated Diels–Alder reactions: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (b) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 455–483. (c) Bonnesen, P. V.; Puckett, C. L.; Honeychuck, R. V.; Wersh, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6070 and references therein.

[3] For leading references to spectroscopic studies, see: (a) Faller, J. W.; Ma, Y. *J. Am. Chem. Soc.* **1991**, *113*, 1579. (b) Reetz, M. T.; Hullman, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (c) Crist, D. R.; Hsieh, A.-H.; Quicksall, C. O.; Sun, M. K. *J. Org. Chem.* **1984**, *49*, 2478–2483. (d) Crist, D. R.; Hsieh, Z.-H.; Jordan, G. J.; Schinco, F. P.; Maciorowski, C. A. *J. Am. Chem. Soc.* **1974**, *96*, 4932–4937. (e) Grinvald, A.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 94–98. (f) Olah, G. A.; Calin, M.; O'Brien, D. H. *J. Am. Chem. Soc.* **1967**, *89*, 3586.

[4] For examples of crystal structures of planar enone–Lewis acid complexes, see refs 3a–c, 11, and the following: (a) Honeychuck, R. V.; Bonnesen, P. V.; Farahi, J.; Hersh, W. *J. Org. Chem.* **1987**, *52*, 5296. (b) Lewis, F. D.; Oxman, J. D.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 466–468. (c) Murray-Rust, P.; Glusker, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1018–1025.

[5] (a) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127. (b) Laszlo, P.; Teston, M. *J. Am. Chem. Soc.* **1990**, *112*, 8750. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. (d) LePage, T. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 6642. (e) Guner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1987**, *52*, 3974. (f) Nelson, D. J. *J. Org. Chem.* **1986**, *51*, 3185–3186. (g) Raber, D. J.; Raber, N. K.; Chandrasekhar, J.; Schleyer, P. v. R. *Inorg. Chem.* **1984**, *23*, 4076–4080.

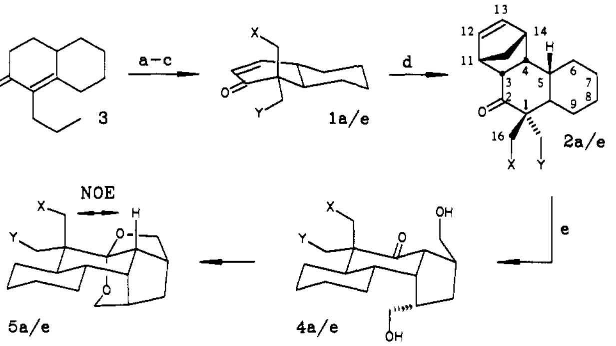
[6] Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

[7] Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101.

[8] Models were constructed assuming Ti–O and Ti–Cl bond lengths of 2.1 and 2.26 Å, respectively; see ref 9a.

0002-7863/91/1513-8973$02.50/0

Scheme I[a]



[a] **a**: X = OCH_3, Y = Et. **e**: X = Et, Y = OCH_3. (a) Li/NH_3; then Me_3SiCl/Et_3N, THF, −15 °C, 90%; (b) $ClCH_2OCH_3$, cat. $ZnBr_2$, CH_2Cl_2, 86%, ca. 6:1 ratio of axial/equatorial CH_2OCH_3; (c) LDA, −78 °C; then PhSeBr; then H_2O_2, EtOAc/H_2O, 71% from either isomer; (d) 1.0 equiv of $TiCl_4$, 10 equiv of cyclopentadiene, CH_2Cl_2, −30 °C, 18–24 h; 44% **2a** + 44% recovered starting material for **1a**, 35% **2e** + 56% recovered starting material for **1e**; (e) O_3, CH_2Cl_2, −78 °C; then 0.75 equiv of $NaBH_4$, EtOH/CH_2Cl_2, 41% for either isomer.

of in-plane complexes of $TiCl_4$ are known,[9-14] Helmchen has reported the crystal structure of an acrylate ester complex in which the titanium is oriented toward a π-type geometry to a significant degree.[9a] The stereochemistries of the Diels–Alder products from the complex are consistent with a similar geometry in solution.[15,16]

The synthesis of **1e** and **1a** is outlined in Scheme I.[17,18] Addition of $TiCl_4$ to 0.020 M CD_2Cl_2 solutions of **1e** results in the progressive downfield shift of the ^1H NMR resonances of the β-enone and methoxy protons.[19] These increases stop abruptly at 1.0 equiv of $TiCl_4$ and remain unchanged upon continued addition to 2 equiv. We interpret this behavior as being due to formation of a 1:1 complex involving coordination to both carbonyl and methoxy oxygens. Titration of **1a** with $TiCl_4$ gave similar results.[20]

Cyclopentadiene reacts with both **1a** and **1e** from the α-face to give the endo adducts **2a** and **2e**, respectively, as the sole products. The ca. 4 Hz coupling constants observed between H_{C11} and H_{C3} and between H_{C14} and H_{C4} in **2a** and **2e** suggests an endo geometry of the cycloadduct.[21,22] Ozonolysis of **2a** followed by treatment with 0.75 equiv of $NaBH_4$ gave keto diol **4a**, which spontaneously cyclized to the pentacyclic ketal **5a**. The ready cyclization of **4a** and the observation of a 1.5% NOE enhancement of the axial H_{C3} in the ^1H NMR spectrum upon irradiation of H_{C16} are consistent only with cycloaddition from the α-face of **1a**. The stereochemistry of **2e** is assigned by analogy to that of **2a**; the H_{C4}–H_{C5} coupling constants in **2a** and **2e** are identical (8.4 Hz), and **2e** may be converted to a pentacyclic ketal **5e** which has ^1H and ^{13}C NMR spectra nearly identical to those of **5a**.

The relative rates of reaction of **1a**·$TiCl_4$ and **1e**·$TiCl_4$ with cyclopentadiene were determined by competition experiments;[23] cyclopentadiene (10 equiv) was added to −30 °C CH_2Cl_2 solutions which were 0.020 M in **1a**, 0.020 M in **1e**, and 0.040 M in $TiCl_4$. At appropriate intervals[24] the reactions were quenched and analyzed by HPLC. We find that the presumed π-complex **1a**·$TiCl_4$ reacts 15.0 ± 0.2[25] times faster than the presumed in-plane complex **1e**·$TiCl_4$. Thus, contrary to conventional expectations, it appears that *an in-plane complexation geometry is less effective in activating the enone toward a Diels–Alder reaction than an out-of-plane geometry, in which $TiCl_4$ may interact directly with the π-system.*

An alternative interpretation of these results is that the reaction of **1a**·$TiCl_4$ proceeds via a small concentration of a nonchelated complex with a monodentate $TiCl_4$ coordinated in the plane of the carbonyl; this species would presumably be more reactive than the enone complex **1e**·$TiCl_4$ in which the titanium is chelated, since $TiCl_4$ should be a stronger Lewis acid than R_2O·$TiCl_4$. We find this scenario unlikely. The difference in reactivity would have to be very large, as our titration studies suggest that the concentration of such a species would be quite small. Furthermore, steric hindrance from the propyl group should direct $TiCl_4$ complexation syn to the alkene; in this position it should represent significant steric hindrance to a Diels–Alder reaction. In this regard it is of note that neither **1a** nor **1e** reacts with cyclopentadiene in the presence of BF_3 or $AlCl_3$; neither of these strong Lewis acids is subject to chelation, and both would be expected to be coordinated syn to the alkene. Another possibility is that the conformation of **1a**·$TiCl_4$ becomes distorted toward a boat so as to allow an in-plane complexation geometry; the reaction of the complex might be accelerated by relief of strain upon going to the products. If this were the case, then the relative binding affinity of **2a** vs **2e** for $TiCl_4$ would be expected to increase as compared to that of **1a** vs **1e**; the opposite is true.[26] Furthermore,

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(9) Crystal structures of $TiCl_4$ having some degree of π-type geometry: (a) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112. (b) Bassi, I. W.; Calcaterra, M.; Intrito, R. *J. Organomet. Chem.* **1977**, *127*, 305.

(10) Crystal structures of in-plane complexes: (a) Brun, L. *Acta Crystallogr.* **1966**, *20*, 739. (b) Maier, G.; Seipp, U. *Tetrahedron Lett.* **1987**, *28*, 4515. (c) Utka, J.; Sobota, P.; Lis, T. *J. Organomet. Chem.* **1987**, *334*, 341.

(11) A review dealing with aspects of in-plane complexes and π-complexes has recently appeared: Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256.

(12) For η^2 complexes of enones with other transition metals, see: (a) Einstein, F. W. B.; Jones, R. H.; Klahn-Oliva, A. H.; Sutton, D. *Organometallics* **1986**, *5*, 2476. (b) Grevels, F.-W.; Lindemann, M.; Benn, R.; Goddard, R.; Kruger, L. *Z. Naturforsch.* **1980**, *35B*, 1298. (c) Herrmann, W. A. *Chem. Ber.* **1975**, *108*, 486. (d) Kruck, T.; Knoll, L. *Chem. Ber.* **1973**, *106*, 3578. (e) Grevels, F.-W.; Schulz, D.; Gustorf, E. K. von *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 534. (f) Tate, D. P.; Buss, A. A.; Augl, J. M.; Ross, B. L.; Grassell, J. G.; Ritchey, W. M.; Knoll, F. J. *Inorg. Chem.* **1965**, *4*, 1323.

(13) For leading references to η^2 complexes of transition metals with nonconjugated aldehydes and ketones, see: (a) Harman, W. D.; Fairlie, D. P.; Taube, H. *J. Am. Chem. Soc.* **1986**, *108*, 8223. (b) Garner, C. M.; Mendez, N. Q.; Kowalczyk, J. J.; Fernandez, J. M.; Emerson, K.; Larsen, R. D.; Gladysz, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 5146. (c) Fernandez, J. M.; Emerson, K.; Larsen, R. H.; Gladysz, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 8268.

(14) For η^4 transition-metal complexes, see refs 12d,e and the following: (a) Zhang, W.-Y.; Jakiela, D. J.; Maul, A.; Knors, C.; Lauher, J. W.; Helquist, P.; Enders, D. *J. Am. Chem. Soc.* **1988**, *110*, 4652 and references therein. (b) Stark, K.; Lancaster, J. E.; Murdoch, H. D.; Weiss, E. *Z. Naturforsch.* **1964**, *19B*, 284. (c) Moriarty, R. E.; Ernst, R. D.; Bau, R. *J. Chem. Soc., Chem. Commun.* **1972**, 1242. (d) King, R. B.; Fronzaglia, A. *J. Chem. Soc., Chem. Commun.* **1966**, 274. (e) Cian, P. A.; Weiss, R. *Acta Crystallogr.* **1972**, *B28*, 3273.

(15) Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *25*, 2191.

(16) Diels–Alder reactions of structurally similar acrylate esters: (a) Helmchen, G.; Hady, A. F. A.; Hartmenn, H.; Karge, R.; Krotz, A.; Sartor, K.; Urmann, M. *Pure Appl. Chem.* **1989**, *61*, 409. (b) Poll, T.; Hady, A. F. A.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. *Tetrahedron Lett.* **1989**, *30*, 5595. (c) Hartmann, H.; Hady, A. F. A.; Sartor, K.; Weetman, J.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1143. (d) Poll, T.; Sobczak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095.

(17) All new compounds had satisfactory spectroscopic data and combustion analyses or high-resolution mass spectra; full details of the syntheses and characterizations of **1–5** are available in the supplementary material.

(18) Compound **3** was synthesized in 42% yield from the annulation of the morpholine enamine of cyclohexanone with 1-hepten-3-one; see the supplementary material.

(19) ^1H NMR chemical shifts of **1e** vs **1e**·$TiCl_4$: δ 3.25 vs 4.16 (OCH_3), δ 6.56 vs 7.28 (β-enone proton). The changes in chemical shifts in both the ^1H and ^{13}C NMR spectra are typical of other enones complexed with Lewis acids: (a) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801. (b) Fratiello, A.; Stover, C. S. *J. Org. Chem.* **1975**, *40*, 1244. (c) Hartman, J. S.; Stilbs, P.; Forsen, S. *Tetrahedron Lett.* **1975**, 3497.

(20) ^1H NMR chemical shifts of **1a** vs **1a**·$TiCl_4$: δ 3.18 vs 3.90 (OCH_3), δ 6.60 vs 7.41 (β-enone proton).

(21) Marchand, A. P.; Rose, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 3724 and references therein.

(22) Endo addition to substituted 2-cyclohexenones is generally observed: (a) Angell, E. C.; Fringuelli, F.; Guo, M.; Minuti, L.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1988**, *53*, 4325. (b) Angell, E. C.; Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642. (c) Grieco, P. A.; Vidari, G.; Ferrino, S. *Tetrahedron Lett.* **1980**, *21*, 1619.

(23) Measurements of absolute rate constants were precluded by competing polymerization of the cyclopentadiene. Such polymerization is not uncommon; see refs 2c, 15, and 22c.

(24) Reactions were quenched at low overall conversions (ca. 10%) to avoid significant change in reactant concentration.

(25) Result of four determinations; two additional experiments using 1.25 equiv of $TiCl_4$ gave reactivity ratios of 15.0 and 14.9.

any distortion of the enone from planarity would be expected to *decrease* the reactivity through loss of conjugation.

Our results, in conjunction with Helmchen's work (vide supra), provide strong evidence that the *reactive* geometry of $TiCl_4$–enone complexes may be of an out-of-plane type; further work will be required to establish whether this is a general phenomenon. These results do not, of course, imply that a preference for an out-of-plane reactive geometry exists for other Lewis acids; $TiCl_4$ may be unique in this regard. However, our results do point out the need for caution in basing predictions of reactive geometries on X-ray and spectroscopic data.

Acknowledgment. Financial support by the National Science Foundation (CHEM-8813618) and by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Supplementary Material Available: Details of the synthesis and characterization of compounds **1–5** as well as the kinetics procedures (13 pages). Ordering information is given on any current masthead page.

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(26) ^1H NMR competition experiments employing 1/1/1 **1a**/**1e**/$TiCl_4$ and **2a**/**2e**/$TiCl_4$ indicated a 14/86 ratio of **1a**·$TiCl_4$/**1e**·$TiCl_4$, but that **2a** does not effectively compete with **2e** for $TiCl_4$ (only **2e**·$TiCl_4$ present). We thank a referee for suggesting this experiment.

[1 + 4] Cycloaddition of Vinyl Isocyanates with Alkyl Isocyanides. Formal Total Synthesis of Erysotrine[†]

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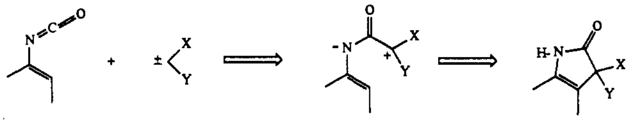
Received August 12, 1991

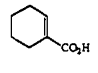
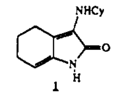
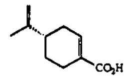
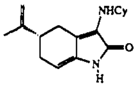
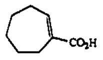
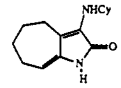
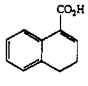
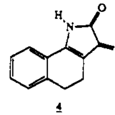
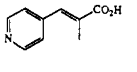
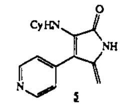
Vinyl isocyanates have emerged as particularly versatile intermediates in combination with various 1,2-dipole equivalents for the construction of structurally elaborate pyridine systems.[1] Employing appropriate 1,1-dipolar reaction partners should permit direct access to highly substituted and functionally rich pyrrolinone derivatives as depicted in eq 1.



(1)

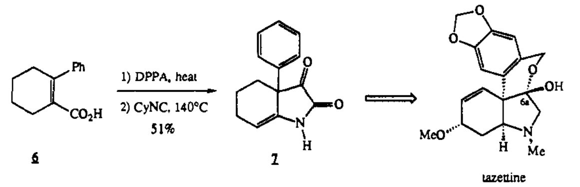
Isocyanides display a unique reactivity profile that is particularly well suited for serving as a 1,1-dipole equivalent in the present context.[2] We report herein that a wide variety of vinyl isocyanates undergo a highly efficient, room temperature [1 + 4] cycloaddition[3] with readily available cyclohexyl isocyanide (CyNC) to produce substituted pyrrolinone derived products. Several examples illustrating the scope of this novel cycloaddition are compiled in Table I.

Table I. Reaction of Vinyl Isocyanates with Cyclohexyl Isocyanide

Entry	Acid	Product[a]	Yield (%)
1		 **1**	84
2		 **2**	68
3		 **3**	75
4		 **4**	82
5		 **5**	81

[a] Each product displays spectral (^1H NMR, ^{13}C NMR, IR, MS) and analytical (HRMS and/or combustion analysis) data in complete accord with the assigned structure.

Typically, the isocyanate reaction partner is generated in nearly quantitative yield from the corresponding α,β-unsaturated carboxylic acid by treatment with diphenyl phosphorazidate (DPPA)[4] followed by heating in acetonitrile. This reaction mixture is then cooled, a slight excess of cyclohexyl isocyanide[5] is added, and the resultant mixture is stirred at room temperature for 15 h. In most cases the product precipitates from the reaction mixture and is isolated by filtration and recrystallization.



(2)

In light of the widespread occurrence of the hydroindole unit as a substructure in numerous alkaloid families, this methodology, which can accommodate substantial structural modifications, should prove of considerable utility for the rapid assembly of a range of target natural products. As a particularly stringent test of the scope of this process for carbon–carbon bond formation in the face of significant steric hindrance and as a model for the construction of the *Sceletium* alkaloids (mesembrine), the isocyanate derived from carboxylic acid **6**[6] was exposed to cyclohexyl isocyanide (CyNC) under normal conditions. While no cycloaddition was detected at room temperature, the cyclization proceeded smoothly in refluxing xylene to give adduct **7**[7] (mp 186–188 °C) in 51% overall yield. The functionalization available in intermediate **7** is particularly significant with regard to the eventual construction of certain Amaryllidaceae alkaloids such as tazettine.[8]

The Amaryllidaceae alkaloid ring system can also be rapidly accessed by employing this [1 + 4] protocol starting from building block **1** (Table I). Chemoselective N-alkylation of the enamide

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[†] Portions of this work were reported at the Symposium on Heterocycles in Synthesis, 200th National Meeting of the American Chemical Society, Washington, DC, August 29, 1990, ORGN 202.

(1) (a) Rigby, J. H.; Qabar, M. *Synth. Commun.* **1990**, *20*, 2699. (b) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852. (c) Rigby, J. H.; Holsworth, D. D.; James, K. *Ibid.* **1989**, *54*, 4019. (d) Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1989**, *54*, 224.

(2) (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (b) Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L. *J. Org. Chem.* **1990**, *55*, 1721. (c) Westling, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1987**, *109*, 590. (d) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159. (e) Deyrup, J. A.; Killion, K. K. *J. Heterocycl. Chem.* **1972**, *9*, 1045.

(3) For some recent examples of other 1 + 4 strategies into nitrogen heterocycles, see: (a) Pearson, W. H.; Bergmeier, S. C.; Degan, S.; Lin, K.-C.; Poon, Y.-F.; Schkeryantz, J. M.; Williams, J. P. *J. Org. Chem.* **1990**, *55*, 5719. (b) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041. (c) Bäckvall, J. E.; Renko, Z. D.; Byström, S. E. *Ibid.* **1987**, *28*, 4199.

(4) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.

(5) Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 300.

(6) Klein, J.; Levin, G. *J. Am. Chem. Soc.* **1958**, *80*, 1707.

(7) This compound displayed spectral (^1H NMR, ^{13}C NMR, IR, MS) and analytical (combustion analysis and/or HRMS) data in complete accord with the assigned structure.

(8) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.

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