cluded either in calculated positions or else in positions obtained from a difference Fourier map, and non-hydrogen atoms were assigned anisotropic thermal parameters. Final residuals were $R = 0.040$ and $R_w = 0.045$.

Acknowledgment. This work was supported by the Auckland Division of the Cancer Society of New Zealand and by the Medical Research Council of New Zealand.

Registry No. **5a**, 117860-53-4; **5b**, 117860-54-5; **6**, 3112-31-0; **7**, 33146-99-5; **8a**, 117860-55-6; **8b**, 117860-56-7; **9**, 75092-39-6; **10a**, 117860-57-8; **10b**, 117860-58-9; **11a**, 92406-53-6; **11b**, 89088-56-2; **12a**, 117860-59-0; **12b**, 117860-60-3; 3,5-dimethylpyrazole, 67-51-6.

Supplementary Material Available: Atomic coordinates, bond lengths, and bond angles for **11a** (2 pages). Ordering information is given on any current masthead page.

A New Versatile Synthesis of Oxazoles by Intramolecular Aza-Wittig Reaction[1]

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Received August 10, 1988

A new synthesis of oxazoles by an intramolecular aza-Wittig reaction is described. Readily available α-azido ketones **2** were converted to (*Z*)-β-(acyloxy)vinyl azides **3** by selective enol acylation. These vinyl azides **3** reacted with triethyl phosphite to afford the corresponding oxazole derivatives **5** via the Staudinger reaction, followed by an intramolecular aza-Wittig reaction. In particular, this oxazole synthesis was useful for oxazoles having acid-labile substituents.

Azido functionality is very useful in the synthesis of various types of nitrogen compounds including nitrogen heterocycles.[2] For example, the ready and clean generation of iminophosphoranes, aza ylides, via the Staudinger reaction,[3] and their utility for synthesis of compounds containing carbon–nitrogen double bonds (or single bonds) via the aza-Wittig-type reaction are well recognized.[4,5] The intramolecular version of the aza-Wittig reaction should have a high potential for the synthesis of nitrogen heterocycles. However, synthetic applications of this methodology for nitrogen heterocyles have drawn increasing attention only recently.[6,7] Among these applications, there are reports in which 2-(acyloxy)phenyl azides reacts with triethyl phosphite to afford 2-substituted benzoxazoles (eq 1)[6a] but the reaction with hexamethylphosphorous triamide leads to the 1,3,2-benzoxazaphosphole derivative.[6c] These

Table I. α-Azido Ketones 2 from α-Bromo Ketones 1

2[a]	R_1	R_2	yield,[b] %	mp, °C
a	Ph	H	86	oil
b	*p*-ClC_6H_4	H	92	67–70
c	*p*-BrC_6H_4	H	90	79.5–81
d	*p*-MeC_6H_4	H	80	59–62
e	*p*-$MeOC_6H_4$	H	97	71–73
f	2-furyl	H	86	32–33
g	Ph	Me	80	oil
h	Ph	*i*-Pr	98	oil

[a] C, H, N analyses were within 0.3% of calculated values. [b] Isolated yields.

Table II. (Acyloxy)vinyl Azides 3 by Enol Acylation

entry	3[a]	R_1	R_2	R_3	yield,[b] %	mp, °C
1	**a**	Ph	H	Me	77	60[d]
2	**b**	*p*-ClC_6H_4	H	Me	55	87[d]
3	**c**	*p*-BrC_6H_4	H	Me	71	82[d]
4	**d**	*p*-MeC_6H_4	H	Me	60	46[d]
5	**e**	*p*-$MeOC_6H_4$	H	Me	79	74[d]
6	**f**	2-furyl	H	Me	67	34[d]
7	**g**	Ph	Me	Me	62	oil
8	**h**	Ph	*i*-Pr	Me	16	33–37
9	**i**	Ph	H	Et	84	oil
10	**j**	Ph	H	cyclopropyl	59	61[d]
11	**k**	Ph	H	Ph	trace	47[d]
12	**k**				43[c]	
13	**l**	Ph	H	2-furyl	72[c]	68[d]
14	**m**	Ph	H	3-pyridyl	14[c]	80[d]
15	**n**	2-furyl	H	2-furyl	67[c]	oil

[a] C, H, N analyses were within 0.3% of calculated values. [b] Isolated yields. [c] Addition of 1 equiv of HMPA. See Experimental Section. [d] Decomposition.

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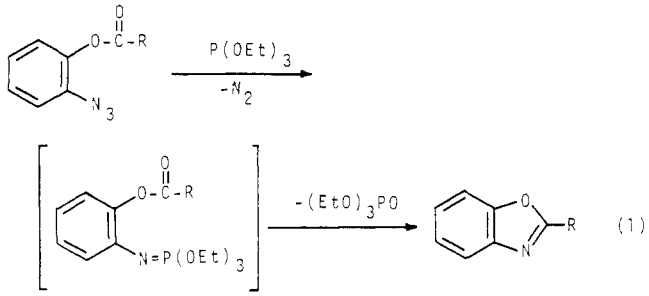
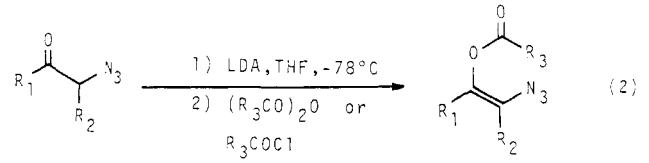


(1)

examples indicate an interesting effect of the substituents on phosphorus in aza-Wittig reactions. As an extension of our studies on intramolecular aza-Wittig reactions,[7] we have examined the reactions of β-(acyloxy)vinyl azides with phosphorus(III) reagents, which provided a new versatile synthesis of 2,5-di- and 2,4,5-trisubstituted oxazole derivatives. We describe here these results in detail.

Results and Discussion

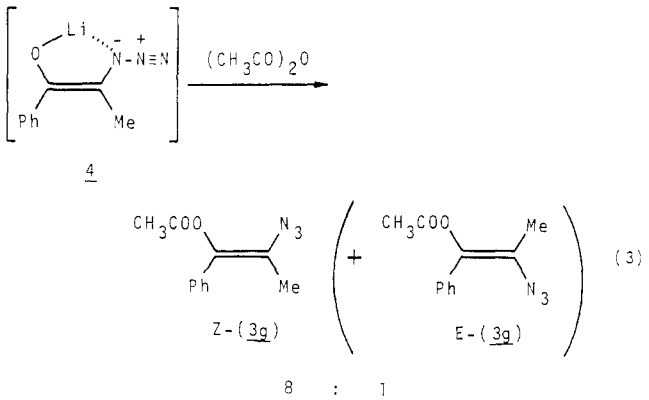
Synthesis of β-(Acyloxy)vinyl Azides 3. The required β-(acyloxy)vinyl azides **3** were prepared by the sequence shown in eq 2. Readily available α-bromo ketones



(2)

2 **3**

1 were converted to the corresponding α-azido ketones **2** by treatment with sodium azide in dimethyl sulfoxide at room temperature in the yields shown in Table I. Exclusive enol acetylations of **2** were successfully carried out by treatment with lithium diisopropylamide (LDA) at −78 °C in THF, followed by addition of acetic anhydride to afford β-acetoxyvinyl azides **3a–h** in good yields (Table II). In the case of **3g** (R_1 = Ph, R_2 = Me), the *Z*/*E* isomer ratio was determined to be 8:1 by ^{1}H NMR spectroscopy. All other products of **3** were of the *Z* configuration on the basis of their ^{1}H NMR spectra and the fact that the corresponding oxazoles were obtained in good yields as described below. The observed *Z* selectivity required for intramolecular aza-Wittig reaction is rationalized in terms of the chelation effect of lithium cation on the α-nitrogen of the azido group (eq 3). The much lower yield of **3h** may



(3)

4

Z-(3g) : E-(3g) = 8 : 1

be due to steric hindrance of isopropyl group destabilizing both *Z* and *E* isomers, although the isolated **3h** consisted of the *Z* isomer (^{1}H and ^{13}C NMR data and cyclization to oxazole **5h**). (Acyloxy)vinyl azides **3i–n** were similarly

Table III. Reaction of 3a with Phosphorus(III) Reagents[a]

entry	phosphorus reagent	temp, °C	yield of 7a,[b] %
1	10 equiv of $P(OEt)_3$	90	87
2	1 equiv of $P(OEt)_3$	90	49
3	10 equiv of $P(OEt)_3$	rt	60
4	10 equiv of PPh_3	90	67
5	10 equiv of PBu_3	90	19

[a] See Experimental Section for a detailed procedure. [b] Isolated yield.

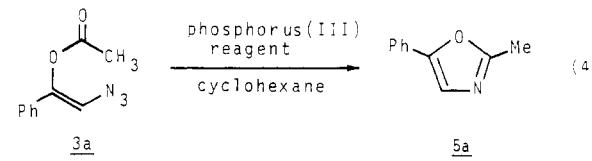
Table IV. Oxazoles 5 by the Reaction of 3 with $P(OEt)_3$

entry	5[a]	yield,[b] %	mp, °C
1	a	87	55–57[d,e]
2	b	80	57–59[e,f,g]
3	c	88	83–85[e]
4	d	93	53–56[e]
5	e	74	105–106[e]
6	f	61	oil
7	g	69	49–51[h]
8	g	70[c]	
9	h	56	oil
10	h	58[c]	
11	i	64	oil
12	j	61	34–36.5
13	k	84	71–73[d]
14	l	48	64–67
15	m	74	86–87
16	n	55	58.5–59.5

[a] C, H, N analyses were within 0.3% of calculated values. [b] Isolated yields. [c] The reaction were performed under room temperature. [d] See ref 16a. [e] See ref 16b. [f] See ref 16c. [g] See ref 16d. [h] See ref 16e.

obtained by using other acid anhydrides or acid chlorides (Table II). However, (benzoyloxy)vinyl azide (**3k**) from **2a** was obtained only in very low yield under these conditions. It is well-known that C- and O-benzoylation of acetone enolate depends on the reaction conditions,[8] and O-acylation is favored in dipolar aprotic solvents.[9] Thus, addition of HMPA (1 equiv) to the enolate prior to benzoylation improved the yield of **3k** to 43%. Other acyloxylations (entries 13–15) were carried out in the presence of HMPA. (Nicotinoyloxy)vinyl azide (**3m**) was obtained only in low yield even under these conditions presumably due to the insolubility of nicotinoyl chloride hydrochloride.

Intramolecular Aza-Wittig Reaction of β-(Acyloxy)vinyl Azides 3. The reactions of **3a** with triethyl phosphite, triphenylphosphine, and tributylphosphine were examined in cyclohexane at room temperature for 1 h, followed by heating at 90 °C for 24 h. Nitrogen evolution via the Staudinger reaction had ceased during the first 1 h, but heating was needed for completion of the intramolecular aza-Wittig reaction in a reasonable time (24 h) to afford 2-methyl-5-phenyloxazole (**5a**) (eq 4, Table III).



(4)

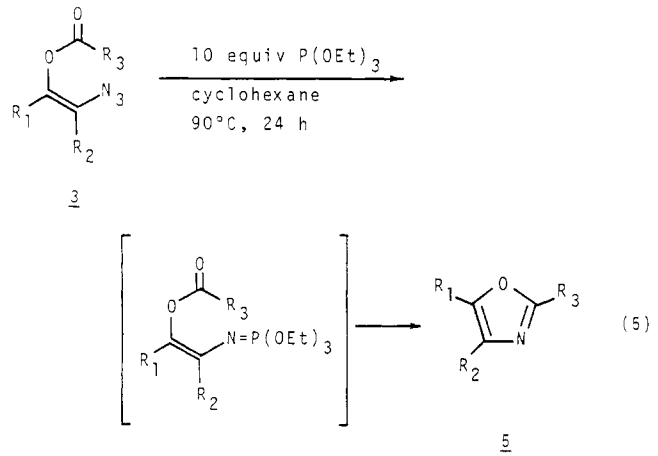
3a **5a**

The use of a 10-fold excess of triethyl phosphite gave better yields after 24 h, although a 60% yield of **5a** was obtained even at room temperature after 24 h (entries 1–3). Among

(8) Muir, W. M.; Ritchie, P. D.; Lyman, D. J. *J. Org. Chem.* **1966**, *31*, 3790.

(9) (a) House, H. O. *Modern Synthetic Reactions*; Benjamin, Inc.: Menlo Park, 1972; Chapter, 5, pp 521–523, 527–530, and references cited therein. (b) Gutmann, V. *The Donor-Acceptor Approach to Molecular Interaction*; Plenum Press: New York, 1978; Chapter 14.

three phosphorus(III) reagents, triethyl phosphite gave better results (entries 1, 4, 5). The reaction with tributylphosphine gave only a 19% yield due to side reactions. The reactions of other (acyloxy)vinyl azides, therefore, were carried out under these conditions by using triethyl phosphite (10 equiv) at 90 °C (24 h). The corresponding aza-Wittig products, oxazole derivatives **5**, were obtained in moderate to good yields (eq 5, Table IV). The



3 5 (5)

reactions of **3g** (R_2 = Me) and **3h** (R_2 = *i*-Pr) afforded oxazoles **5g** and **5h** in 70% and 58% yields, respectively, even at room temperature for 24 h. The steric interaction between an α-alkyl substituent and the phosphorus group may favor the aza-Wittig reaction under milder conditions, as the phosphorylimino group is closer to the carbonyl group.

Oxazoles have drawn renewed interest recently by their usefulness as bloking groups or synthetic intermediates[10,11] and also by their presence in natural products such as alkaloids (texamine, texaline etc)[10,12] and macrocyclic antibiotics.[10] In many prior oxazole syntheses,[10] strong dehydrating reagents (P_2O_5, H_2SO_4, $SOCl_2$, etc.) or Lewis acids are usually required. In our conditions using $P(OEt)_3$ instead of acidic reagents, furyl- or pyridyl-substituted oxazole derivatives such as **5f,l–n** (Table IV) were readily obtainable. An oxazole synthesis via *N*-acylaminophosphonium salts starting from α-azido ketones, triphenylphosphine, and acyl halides reported previously by Zbiral and co-workers[6b] belongs to the so-called type A synthesis using the O–C–C–N–C atomic unit for the ring construction. The present intramolecular aza-Wittig approach is classified as a type B synthesis using the N–C–C–O–C unit.[10a] Both approaches are useful for oxazole synthesis under mild, nonacidic conditions, although yields seem to be better when the present approach is used due to fewer side reactions.

In summary, oxazole derivatives can be prepared from β-(acyloxy)vinyl azides by the intramolecular aza-Wittig reaction. This method has an obvious advantage for synthesis of acid-labile oxazole derivatives. It should be noted also that β-(acyloxy)vinyl azides are new *O*-functionalized vinyl azides that may have reasonable synthetic potential.[13]

Experimental Section

Melting points were measured with a Yanagimoto micro melting point hot stage apparatus and are uncorrected. IR spectra were obtained on a JASCO IRA-1 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-C-60HL instrument at 60 MHz (^1H) and a Varian Gemini 200 instrument at 200 MHz (^1H) and 50 MHz (^{13}C). Chemical shifts are reported in parts per million (ppm) relative to Me_4Si as an internal standard, and coupling constants are in herz. Microanalyses were performed with a Perkin-Elmer 240B elemental analyzer. Column chromatography was performed on Fuji-Davison silica gel BW-300.

α-Bromo ketones **1a,b** are commercially available. Compounds **1c,d,f,g** were prepared from the corresponding ketones with bromine by the standard procedure.[14] Compound **1e** was prepared from the trimethylsilyl enol ether of *p*-methoxyacetophenone with *N*-bromosuccinimide.[15]

General Procedure for Synthesis of α-Azido Ketones 2. To a stirred solution of sodium azide (3.00 mmol) in dimethyl sulfoxide (dried over 4A molecular sieves, 5.0 mL) was added α-bromo ketone **1** (1.00 mmol) at room temperature. After vigorous stirring was continued for 7 min, the mixture was poured onto ice–water and extracted with ether (5 × 30 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a crude azide, which was purified on a silica gel column, eluting with an ethyl acetate–hexane system [1:8 v/v for **2a–e, g**; 1:4 for **2f**; 1:10 for **2h**] to provide analytically pure azido ketones.

Synthesis of α-(Acyloxy)vinyl Azides 3 via Enol Acylation of 2. General Procedure. To a stirred solution of LDA (1.10 mmol) in anhydrous THF (5.0 mL) was added a solution of α-azido ketone **2** (1.00 mmol) in THF (2.0 ml) at −78 °C under argon. In the case of entries 4–7 in Table II, anhydrous HMPA (1.00 mmol) was also added. After the stirring was continued for 1 h at the same temperature, 2 equiv of acid anhydride (for **3a–h,k**) or acid chloride (for **3i,j,l–n**) was added to the mixture, and after 10 min, the mixture was slowly warmed to room temperature while the stirring was continued. After 10 min, the mixture was poured onto ice–water and extracted with ether (5 × 30 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The obtained residue was chromatographed on a silica gel column, eluting with an ethyl acetate–hexane system [1:10 for **3a,g**; 1:4 for **3b,c,e,f,j,l,n**; 1:8 for **3d,i,k**; 1:20 for **3h**; 1:2 for **3m**] to afford analytically pure vinyl azides **3**.

2-Azido-1-phenylvinyl Acetate (3a). To a stirred solution of LDA (2.71 mmol) in anhydrous THF (12.0 mL) was added a solution of α-azidoacetophenone **2a** (400 mg, 2.48 mmol) in THF (5.0 mL) at −78 °C under argon. After the stirring was continued for 1 h, acetic anhydride (510 mg, 5.00 mmol) was added to the dark red mixture, and after 10 min, the mixture was slowly warmed to room temperature while the stirring was continued. After 10 min, the yellowish mixture was poured onto ice–water and extracted with ether (5 × 50 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The obtained yellowish residue was chromatographed on a silica gel column, eluting ethyl acetate–hexane (1:10), to afford 387 mg (76.7%) of **3a** as pale yellow crystals: mp 60 °C dec; IR (CH_2Cl_2) 2110, 1775, 1655 cm^{-1}; NMR δ 7.32 (s, 5 H), 6.56 (s, 1 H), 2.31 (s, 3 H). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.36; H, 4.66; N, 20.54.

2-Azido-1-phenyl-1-propenyl Acetate (3g). This enol acetate **3g** was obtained as a 8.2:1.0 *Z*/*E* mixture by the above procedure. The ^1H NMR spectrum at 200 MHz had singlet peaks at δ 2.194, 2.152, 2.134, and 2.114 due to acetyl and vinyl Me protons. The signals at δ 2.194, 2.114 were assignable to the major *Z* isomer and signals at δ 2.152, 2.134 to the minor *E* isomer. The isomer

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(11) For example, for conversion to azomethine ylides, see: (a) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1988**, *110*, 3238. (b) Vedejs, E.; Grissom, J. W. *J. Org. Chem.* **1988**, *53*, 1876; (c) **1988**, *53*, 1882.

(12) Domínguez, X. A.; de la Fuente, G.; González, A. G.; Reina, M.; Timón, I. *Heterocycles* **1988**, *27*, 35 and references cited therein.

(13) See, for example, Chapter 2 in ref 2b.

(14) Cowper, R. M.; Davidson, L. H. *Organic Syntheses*; Wiley: New York, 1943, Collect Vol. II, p 480.

(15) Oppolzer, W.; Pedrosa, R.; Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831.

ratio was 8.2:1.0 on the basis of these integral ratios.

2-Azido-3-methyl-1-phenyl-1-butenyl Acetate (3h). This enol acetate **3h** was obtained as a single geometrical isomer, which was supported by ^{1}H NMR and ^{13}C NMR spectra: ^{13}C NMR ($CDCl_3$) δ 169.298, 136.982, 134.760, 133.630, 128.844, 128.716, 128.466, 100.400, 28.943, 20.338. The appearance of only 10 lines is compatible with the assigned single isomer.

Syntheses of Oxazoles 5 by Intramolecular Aza-Wittig Reaction of 3. General Procedure. To a stirred solution of β-(acyloxy)vinyl azide **3** (1.00 mmol) in dry cyclohexane (5.0 mL) in a sealed tube was added triethyl phosphite (or other phosphorus(III) reagents) (10.0 mmol). Nitrogen gas evolution started immediately and ceased after 1 h. The mixture was heated at 90 °C for 24 h with continued stirring. The cooled mixture was chromatographed on a short silica gel column, eluting with ethyl acetate–hexane (1:4), to give oxazoles **5**. These products were further purified on a preparative TLC (silica gel, ethyl acetate–hexane 1:4), depending on the purity.

2-Methyl-5-phenyloxazole (5a). To a stirred solution of 2-azido-1-phenylvinyl acetate (**3a**) (150 mg, 0.740 mmol) in dry cyclohexane (4.0 mL) in a sealed tube was added triethyl phosphite (1.23 g, 7.40 mmol). After being stirred at room temperature for 1 h, the colorless mixture was heated at 90 °C for 24 h with continued stirring. The cooled mixture was chromatographed on a silica gel column, eluting with ethyl acetate–hexane (1:4), to give 102 mg (86.8%) of **5a** as white solid: mp 55–57 °C (lit.[16a,b]); IR (CH_2Cl_2) 1590, 1570 cm^{-1}; NMR δ 7.71–7.29 (m, 5 H), 7.19 (s, 1 H), 2.52 (s, 3 H). Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.96; N, 8.61.

Supplementary Material Available: Tables of IR, NMR, and microanalyses data for compounds **2**, **3**, and **5** (5 pages). Ordering information is given on any current masthead page.

(16) (a) Gabriel, S. *Chem. Ber.* **1910**, *43*, 1283. (b) Ibata, T.; Ryohei, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3597. (c) Houwing, H. A.; Wildeman, J.; van Leusen, A. M. *Tetrahedron Lett.* **1976**, 143. (d) Sych, E. P.; Belaya, L. P.; Umanskaya, L. P.; Smaznaya-Il'ina, E. D. *Ukr. Khim. Zh.* **1966**, *32*, 274; *Chem. Abstr.* **1966**, *65*, 2380a. (e) Bhatt, M. V.; Reddy, G. S. *Tetrahedron Lett.* **1980**, *21*, 2359.

Intramolecular Diels–Alder Reaction of α,β-Unsaturated Ester Dienophiles with Cyclopentadiene and the Dependence on Tether Length

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Received September 17, 1987

Cyclopentadiene compounds, tethered to an α,β-unsaturated ester functionality, have been prepared by the direct alkylation of the corresponding iodide or tosylate with cyclopentadienylmagnesium chloride. For example, tso-$CH_2CH_2C(CH_3)_2CH{=}CHCO_2C(CH_3)_3$ reacted with cyclopentadienylmagnesium chloride at 0 °C to yield the alkylated cyclopentadiene, which on heating at 75 °C underwent a Diels–Alder reaction to give an 81% yield of 4,4-dimethyltricyclo[5.2.1.0^{1,5}]dec-8-ene-6-carboxylic acid, *tert*-butyl ester. Isomerization of cyclopentadiene isomers, common with lithium and sodium carbanions, is not displayed with the Grignard reagent. Several functionalized cyclopentadienes have been prepared which differ in tether length. These substrates readily undergo intramolecular [4 + 2] cycloaddition at mild temperatures to produce tricyclic ring systems. The cycloaddition will proceed at even lower temperatures if catalyzed by diethylaluminum chloride. Pathways of cycloaddition favor incorporation of the tether linkage into a five- or six-membered ring.

Introduction

The predictability and selectivity with which the Diels–Alder reaction forms two bonds and four potential asymmetric centers has led to its wide-spread use in synthesis. The intermolecular Diels–Alder reaction has been particularly useful in natural product synthesis, since this reaction has the additional advantages of forming an extra ring, increased reactivity due to entropic factors, and additional regiochemical constraints yielding a marked increase in stereoselectivity and diastereoselectivity.

Cyclopentadiene has been used extensively for the formation of bicyclo[2.2.1]heptane compounds as precursors to natural products.[1c] The occurrence of these naturally occurring bridging sesquiterpenes has led to the development and use of the intramolecular cycloaddition with cyclopentadiene. Subsequent ring expansion of the resulting cycloaddition products has been employed in the total synthesis of several cedrane derivatives, cedrene,[2] cedrol,[2] and cedranediol.[3] The synthesis of sativene has also been achieved through ring expansion of an intramolecular Diels–Alder product.[4] Other examples include the current development of this methodology as an approach to the synthesis of sinularene, longifolene, as well as an alternate route to sativene.[5] Cleavage of the strained olefin, followed by further functional group modification has led to the recent synthesis of two naturally occurring triquinanes,[6] such as siliphinene[7] and capnellene.[8] Recent advances in asymmetric induction of the Diels–Alder reaction[10,11] have made this cycloaddition a promising me-

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