3.32 (s, 1 H), 3.16 (d, 1 H, J = 16.5 Hz), 2.99 (d, 1 H, J = 16.5 Hz); MS m/e 368 (M^+), 328 ($M^+ - CH_2CN$).

Conversion of Oxirane 4b to β-Hydroxy Nitrile 10c. The procedure used to convert oxirane **4a** to **10a** was repeated on oxirane **4b**. β-Hydroxy nitrile **10c** was obtained in 48% yield. This sample was identical with **10c** derived from cleavage of the minor bis(dihydroisoxazole) **8d**.

Reaction of Oxirane 4a with Aqueous 30% $HClO_4$. A solution of **4a** (46.6 mg, 0.13 mmol) and 30% $HClO_4$ (90 μL) in THF–water (3:1, 6 mL) was stirred at room temperature for 24 h under N_2. The resulting solution was diluted with CH_2Cl_2 (10 mL) and was washed with saturated $NaHCO_3$. Further workup gave crude product containing **6a,b** (85:15 **a/b** ratio by NMR) some (4,5-dihydro-4,5-diphenyl-3-isoxazolyl)phenylmethanone and several other unidentified products. Preparative TLC (99:1 CH_2Cl_2–MeOH) provided 32.5 mg (66% yield) of **6a** and 10.1 mg (21% yield) of a mixed fraction (40:60 ratio) of **6a** and **6b**.

Reaction of Oxirane 5a with Aqueous 30% $HClO_4$. A solution of **5a** (26 mg, 0.076 mmol) and 30% $HClO_4$ (50 μL) in THF–water (3:1, 4 mL) was stirred at room temperature for 21 h under N_2. Workup and preparative TLC as described in the previous reaction gave 15.8 mg (58% yield) of a mixture (80:20 **a/b** ratio by NMR) of **6a,b**.

Supplementary Material Available: ^1H NMR spectra of **5a,b**, **6b**, **7**, **8c**, **9a,b**, **d**, **10b**, and **11**, ORTEP drawing of **9c**, crystal data for **9c**, tables of refined positional and thermal parameters for **9c**, and tables of bond lengths and bond angles for **9c** (15 pages). Ordering information is given on any current masthead page.

Diastereofacial Selectivity Studies on 4-Substituted 3-Acyl-4,5-dihydroisoxazoles

Peter A. Wade,*,† David T. Price,† Patrick J. Carroll,‡ and William P. Dailey‡

Departments of Chemistry, Drexel University and the University of Pennsylvania, Philadelphia, Pennsylvania 19104

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Carbonyl addition of organolithium reagents to 3-acyl-4,5-diphenylisoxazoles gave tertiary alcohols with ≥98% diastereomer excess (de) in the two cases examined. Similar carbonyl addition of Grignard reagents also occurred with ≥96% de, but with a preference for the *opposite* stereoisomer. Diastereoselectivities for addition to benzoyl-3a,5,6,6a-tetrahydro-4*H*-cyclopent[*d*]isoxazole were lower (≥86% de). Carbonyl addition to 4,5-diphenyl-4,5-dihydro-3-isoxazolecarboxaldehyde also gave much reduced diastereoselectivity (12–80% de). Reduction of 3-acyldihydroisoxazoles with a series of hydride reagents showed diastereoselectivity, but only 9-BBN gave ≥86% de. These changes in stereoselectivity are rationalized based on a combination of heterodiene conformational preference and attack anti to the 4-substituent. The s-trans conformer of 4,5-dihydro-3-isoxazolecarboxaldehyde was determined by the ab initio method to be 6.8 kcal/mol more stable than the s-cis conformer.

3-Acyl-4,5-dihydroisoxazoles, readily prepared by nitrile oxide cycloaddition to alkenes,[1] are attractive intermediates for the synthesis of carbohydrates. The moderate rigidity of the five-membered ring and the availability of coordination sites at ring N and O atoms (perhaps in conjunction with the carbonyl O atom) suggest the possibility for stereoselective transformation of the carbonyl group. In a preliminary publication,[2] it was demonstrated that very high diastereomer excess (de) and virtually complete stereochemical control were possible by judicious choice of organolithium reagents or Grignard reagents. This, coupled with the known procedures[3,4] for reductive cleavage of the dihydroisoxazole ring, should then provide a new approach to the construction of 2-amino 1,4-diols and 1,2,4-triols. Here more extensive stereochemical studies on acyldihydroisoxazoles and complete experimental details will be presented.

α-Nitro ketones, either directly or as the methyl nitronic esters, cycloadd to (*E*)-stilbene and cyclopentene providing easy access to the dihydroisoxazoles **1a**, **3a**, and **3b**.[5] Dihydroisoxazole **1b** was prepared in 31% yield by methylating the dicyclohexylamine salt of nitroacetone with diazomethane and reacting the resulting nitronic ester with stilbene in the presence of *p*-toluenesulfonic acid. 4,5-Diphenyl-4,5-dihydro-3-isoxazolecarboxaldehyde (**1c**) was prepared by published procedures.[6]

Table I. Addition of Organometallic Reagents to 3-Acyl-4,5-dihydroisoxazoles

substr	organometallic	alcohols	ratio	solvent/temp, °C	yield, %
1a	MeLi	**2a/2b**	99.5:0.5	THF/−78	94
1b	PhLi	**2a/2b**	1:99	THF/−78	82
1a	MeMgBr	**2a/2b**	2:98[a]	CH_2Cl_2/−78	72
1a	MeMgBr	**2a/2b**	20:80	THF/0–5	55
1b	PhMgBr	**2a/2b**	>99:1[b]	CH_2Cl_2/−78	82
1c	MeLi	**2c/2d**	70:30	THF/−78	76
1c	MeMgBr	**2c/2d**	34:66	CH_2Cl_2/0–5	95
1c	PhLi	**2e/2f**	90:10	CH_2Cl_2/−78	70
1c	PhMgBr	**2e/2f**	56:44	CH_2Cl_2/−78	86
3a	MeLi	**4a/5a**	95:5	THF/−78	88
3a	MeMgBr	**4a/5a**	7:93	CH_2Cl_2/−78	78
3b	MeLi	**4b/5b**	59:41[c]	THF/−78	93
3b	MeMgBr	**4b/5b**	49:51[d]	CH_2Cl_2/−78	83

[a] 3:97 at 0–5 °C. [b] Using freshly prepared Grignard reagent; 98:2 at 0–5 °C in ether or CH_2Cl_2. [c] Isolated in 55% and 38% yield (62:38 ratio), respectively, in a previously reported[5] run. [d] 46:54 in a duplicate run.

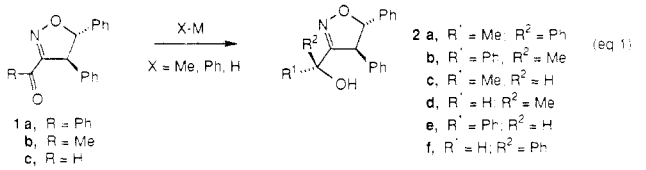
† Drexel University.
‡ University of Pennsylvania.

(1) Grundmann, Ch.; Grünanger, P. *The Nitrile Oxides*; Springer-Verlag: New York, 1971.
(2) Wade, P. A.; Price, D. T.; McCauley, J. P.; Carroll, P. J. *J. Org. Chem.* **1985**, *50*, 2804.

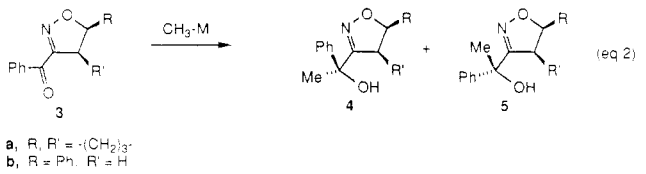
0022-3263/90/1955-3051$02.50/0

Addition of Organolithium Reagents

Carbonyl addition reactions of **1a,b** and **3** have been reported in the preliminary communication.[2] Addition of methyllithium to **1a** gave the diastereomeric alcohols **2a** and **2b** in a 99:1 ratio by HPLC (eq 1 and Table I); the



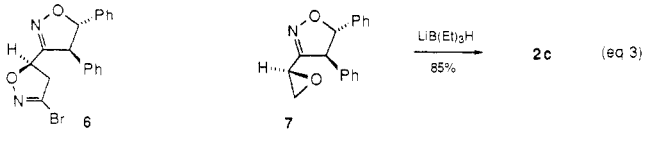
structure of **2a** was based on X-ray data.[2] It was possible to reverse the order of group introduction; phenylation of dihydroisoxazole **1b** gave **2b** and **2a** in a 99:1 ratio. The dihydroisoxazole **3a**, possessing a smaller 4-substituent, reacted with methyllithium to give **4a** and **5a** in a 95:5 ratio (eq 2). Configurational assignments were based on



chemical shift patterns observed for the 4-H ring protons by ^{1}H NMR. Dihydroisoxazoles **2a** and **2b** gave signals at δ 4.18 and 3.98, respectively; thus, the upfield signal was for **2b**. Similarly, **4a** and **5a** gave signals at δ 3.62–3.87 and 3.18–3.34; the upfield signal was for **5a** which then has the same relative configurations at C-4 and C-3α as **2b**. This assignment is predicated on similar conformational preferences for **2b** and **5a**, a likely assumption based simply on steric factors.

Dihydroisoxazole **3b**, which lacks a 4-substituent, showed no facial discrimination; a 59:41 ratio of alcohols **4b** and **5b** was obtained.[7] The configurational assignment was made by analogy to **2a** and **2b**. Structure **5b** was assigned to the isomer exhibiting the more upfield chemical shift for the trans 4H (smaller $J_{4,5}$ than cis 4H): δ 2.69 vs 2.97.

It was of interest to examine carbonyl addition of organolithium reagents to the aldehyde **1c**. Surprisingly, the diastereoselectivity was much decreased compared to the corresponding ketones **1a,b**. Reaction of **1c** with methyllithium at −78 °C gave a 70:30 ratio of diastereomers **2c** and **2d**, which could be chromatographyically separated and the products isolated in 53% and 23% yield, respectively. The structure of **2c** has been assigned by correlation to oxirane **7**; reduction of **7** with lithium triethylborohydride gave **2c** (eq 3). The configuration of **7** has been



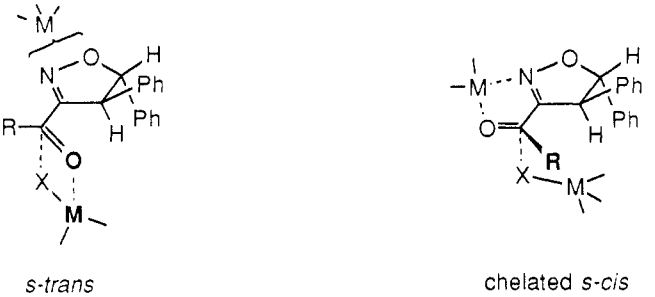
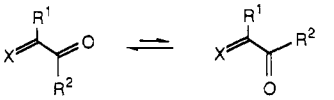


Figure 1. Possible transition states for carbonyl addition and hydride reduction.

Table II. Some Selected s-Trans/s-Cis Ratios for Acyloxime Ethers and 1,2-Diones



X	R¹	R²	s-trans/s-cis
O	H	H	>98:2[a]
O	Me	Me	>98:2[b]
(*E*)-NOEt	Me	Me	>95:5
(*E*)-NOEt	Me	Ph	"s-trans preferred"

[a] s-trans preferred by 5.9 kcal/mol. [b] s-trans preferred by 4.4 kcal/mol.

determined by indirect correlation to bis(dihydroisoxazole) **6**, for which X-ray data were available.[8] Using phenyllithium gave a mixture of **2e** and **2f** (90:10 **2e**/**2f** ratio) in 70% yield. The products could be chromatographically separated, and the structure of **2f** was assigned based on an X-ray study.

The results with organolithium reagents are rationalized based on a nonchelated transition state aggregate having an s-trans N=C—C=O conformation; the lithium atom of the attacking organometallic molecule is presumably coordinated with the carbonyl group (Figure 1). Additional lithium atoms may be coordinated, or even chelated, with the ring nitrogen and oxygen atoms. Facial preference in carbonyl addition is then controlled by the 4-substituent if present and is anti to this substituent.

A strong preference for the ground-state s-trans conformer is anticipated with 3-acyl-4,5-dihydroisoxazoles. Dipole–dipole repulsion between the N and O atoms would disfavor the s-cis conformation. Open-chain *E*-ketooxime ethers[9] and 1,2-diones[10] do show a preference for the s-trans conformation, which, however depends on the groups attached (Table II).

The structures and energies for the s-cis and s-trans conformers of 4,5-dihydro-3-isoxazolecarboxaldehyde (**8**) have been determined using ab initio molecular orbital theory.[11] Both conformers maintained C_s symmetry at the HF/3-21G level in accordance with planar structures. Since the differences in energy between s-trans and s-cis

(3) Conversion to γ-amino alcohols: (a) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79 and references cited therein. (b) Wade, P. A.; Rao, J. A.; Berenzak, J. F.; Yuan, C.-K. *Tetrahedron Lett.* **1989**, *30*, 5969. (c) Wade, P. A.; Price, D. T. *Tetrahderon Lett.* **1989**, *30*, 1185. (d) Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. (e) Müller, I.; Jäger, V. *Tetrahedron Lett.* **1982**, *23*, 4777.

(4) Conversion to β-hydroxy ketones: (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5836. (b) Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023. (c) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

(5) Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595.

(6) Caldirola, P.; De Amici, M.; De Micheli, C.; Wade, P. A.; Price, D. T.; Bereznak, J. F. *Tetrahedron* **1986**, *42*, 5267.

(7) This experiment was previously published, but without assignment of configuration: ref 5.

(8) Wade, P. A.; Bereznak, J. F.; Palfey, B. A.; Carroll, P. J.; Dailey, W. P.; Sivasubramanian, S. *J. Am. Chem. Soc.* preceding paper in this issue.

(9) (a) Baas, P.; Cerfontain, H. *J. Chem. Soc., Perkin Trans.* **2 1977**, 1351. (b) Baas, P.; Cerfontain, H. *J. Chem. Soc., Perkin Trans.* **2 1979**, 151.

(10) (a) Dykstra, C. E.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1975**, *97*, 7210 and references cited therein. (b) Tyrrell, J. *J. Am. Chem. Soc.* **1979**, *101*, 3766.

(11) The calculations employed Gaussian 88: Frisch, M. J.; Head-Gordon, M.; Schlegel, H. B.; Ragavachari, K.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Fluder, E. M.; Topiol, S.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA.

conformations of 3-ethenyl-4,5-dihydroisoxazole at the 6-31G*//6-31G* and 6-31G*//3-21G levels were virtually identical,[8] the latter method was employed with aldehyde **8** for the sake of expediency. Single-point energy calculations at the 6-31G* level of theory gave a total energy of −358.47096 au for the s-trans conformer and −358.45091 au for the s-cis conformer of aldehyde **8**. Thus, the s-trans conformer of **8** is 6.8 kcal/mol more stable than the s-cis conformer. This energy difference would be modified by substituents, but it is unlikely that a significant concentration of the s-cis conformer is present at room temperature in any of the dihydroisoxazoles **1a–c** and **3a,b**.

No one factor occurs to us as a rationale for the change in stereochemical results going from ketones **1a,b** to aldehyde **1c**. Several contributing factors do seem important, however. Since aldehydes in general undergo much more rapid carbonyl addition, it seems likely that less stereoselectivity would be observed for reactions of **1c** ("hot" reactions) than for those of ketones **1a,b**. Perhaps there is a change in the degree of aggregation required for reaction. The modest steric demands of methyllithium, coupled with the "open" carbonyl group of **1c**, might permit a significant degree of syn attack leading to the relatively poor (40% de) selectivity in the reaction of these two reagents.

Addition of Grignard Reagents

The carbonyl addition of Grignard reagents to **1a,b** was also examined. Virtually complete reversal of stereoisomer preference compared to the corresponding organolithium reactions was observed (Table I). Thus, **2a** and **2b** were formed in 72% yield from **1a** but in a 2:98 ratio! Indeed, this is the best approach to preparation of **2b**; the dihydroisoxazole **1b** is less readily available even though it is efficiently converted to **2b**. Reaction of dihydroisoxazole **3a** with methylmagnesium bromide produced predominantly the opposite isomer from the reaction with methyllithium (7:93 **4a**/**5a** ratio).

Grignard addition to aldehyde **1c** was also examined. The diastereoselectivity was again much decreased compared to reactions with the corresponding ketones **1a,b**. Reaction of **1c** with methylmagnesium bromide gave **2c** and **2d** in 28% and 67% yield, respectively. The opposite diastereomer from reaction with methyllithium was preferred; **2d** was formed as the major product (34:66 ratio). Using phenylmagnesium bromide gave a mixture of **2e** and **2f** in 86% yield. Here, **2e**, the *same* major product obtained using phenyllithium, was formed but with a very low stereochemical preference (56:44 **2e**/**2f** ratio).

The stereochemical reversal observed with Grignard reagents compared to organolithium reagents presumably arises from a major change in the preferred transition state, a change attributed to magnesium chelation favoring an s-cis N=C—C=O reacting conformer. Attack anti to the ring C-4 substituent would then afford the opposite stereoisomer. Apparently Grignard reagents have a stronger propensity than organolithium reagents to chelate with 3-acyl-4,5-dihydroisoxazoles. Stronger chelation by magnesium than lithium has been noted elsewhere.[12] Consistent with that hypothesis is the reduced stereoselectivity (only 60% de) observed for reaction of methylmagnesium bromide with **1a** in THF; this solvent could more effectively compete with the dihydroisoxazole for coordination of the organometallic than could methylene chloride, thus lowering the degree of chelation.

(12) For example: Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031.

Table III. Hydride Reduction of 3-Acyl-4,5-dihydroisoxazoles

substr	metal hydride	alcohols	ratio[a]	solvent/ temp, °C	yield, %
1b	$NaBH_4$	**2c**/**2d**	67:33	ethanol/20	89
1b	Li(*sec*-Bu)$_3$BH	**2c**/**2d**	45:55	THF/−78	90
1b	K(*sec*-Bu)$_3$BH	**2c**/**2d**	67:33	THF/−78	70
1b	Al-*i*-Bu$_2$H	**2c**/**2d**	21:79	toluene/−78	74
1b	BH_3·THF	**2c**/**2d**	48:52	THF/0–5	95
1b	9-BBN	**2c**/**2d**	7:93	THF/0–5	90[b]
1a	$NaBH_4$	**2e**/**2f**	50:50[c]	ethanol/20	99
1a	K(*sec*-Bu)$_3$BH	**2e**/**2f**	12:88[c]	THF/0–5	92
1a	Al-*i*-Bu$_2$H	**2e**/**2f**	15:85	toluene/−78	85
1a	9-BBN	**2e**/**2f**	≤1:99[c]	THF/0–5	50[d]

[a] NMR analysis of product mixture; yields are for the purified mixture. [b] After ethanolamine workup and chromatographic purification. [c] Confirmed by separation and isolation of pure **2e** and/or **2f**. [d] After alkaline hydrogen peroxide workup and chromatographic purification.

The high reactivity of Grignard reagents with aldehydes compared to ketones probably plays an important role in determining the low selectivity in carbonyl addition to **1c**. Thus, Grignard reagents might well be sufficiently reactive with **1c** not to require chelation; this is consistent with the observation for phenylmagnesium bromide where **2e** is the major product. The "open" carbonyl group of **1c** might also permit a significant degree of syn attack with Grignard reagents.

Hydride Reductions

The carbonyl reduction of dihydroisoxazoles **1a,b** with a series of hydride reagents has also been studied. Results were obtained using sodium borohydride, lithium tri-*sec*-butylborohydride (L-Selectride), potassium tri-*sec*-butylborohydride (K-Selectride), borane–THF, diisobutylaluminum hydride (DIBAH), and 9-borabicyclo[3.3.1]nonane (9-BBN) (Table III). The highest degree of stereoselectivity was observed in reductions employing 9-BBN. Thus, reduction of dihydroisoxazole **1b** with 9-BBN gave a 93:7 isomer ratio of alcohols **2d** and **2c**. Reaction of **1a** with 9-BBN was highly stereoselective; **2f** was formed in ≥98% de although only in 50% yield. The low yield is largely attributable to difficulty in removing boron from the initial reduction product. DIBAH also gave fair-to-good stereoselectivity with **1b** (79:21 **2d**/**2c** ratio) and **1a** (85:15 **f**/**e** ratio). Somewhat higher stereoselectivity for **1a** compared to **1b** was observed with both 9-BBN and DIBAH.

The high stereoselectivity observed with 9-BBN and to a lesser extent with DIBAH is consistent with strong coordination to form an aggregate and delivery of hydride to the carbonyl C atom of the s-trans conformer. Again, attack was predominantly anti to the 4-phenyl substituent.

Surprisingly, Selectride reagents showed only poor facial discrimination in reactions with **1b**. Reduction with K-Selectride gave markedly different results for dihydroxisoxazoles **1a** and **1b**; a 33:67 isomer ratio of **2d** and **2c** was obtained from **1b** while from **1a** attack was preferentially on the opposite face to produce **2f** and **2e** in an 88:12 ratio.

No evidence for chelation control of stereoselectivity was obtained in most of the hydride reductions. K-Selectride and sodium borohydride did favor formation of **2c** (30% de for both reagents) from **1b**, but these hydride reagents have little ability to chelate.[13] However, the reversed stereoselectivity in the reduction of **1b** with K-Selectride compared to **1a** requires a marked alteration in the pre-

(13) Although K^+ does not often chelate, the complex with 18-crown-6 is one well-known example. Strong chelation with Na^+ is very rare.

ferred transition state; perhaps there is a change from a chelated to nonchelated aggregate. Probably a chelated aggregate would be lower in energy for **1b** than for **1a**; it is sterically preferable to eclipse the ring C-4 atom and acetyl methyl group of **1a** than the corresponding benzoyl phenyl group of **1b**.

Conclusions

A high degree of stereochemical control was possible for the carbonyl addition reactions of 4-substituted 3-acyldihydroisoxazoles. Addition reactions of the corresponding aldehyde gave low (20–80% de) stereoselectivity, but the same products could be obtained stereoselectively (86–96% de) by reduction of the 4-substituted 3-acyldihydroisoxazoles with 9-BBN. Stereocontrol was not obtained in the hydride reductions; only the isomer corresponding to anti attack on the s-trans heterodiene conformation could be prepared efficiently.

The alcohols **2a,b** could be efficiently synthesized via either of two carbonyl addition routes: methylation reactions of dihydroisoxazoles **1a** or phenylation reactions of dihydroisoxazole **1b**. The alcohols **2e–f** could be efficiently synthesized by the proper choice of route. Phenylation of aldehyde **1c** with phenyllithium provided alcohol **2e** in 80% de and 70% yield. Reduction of ketone **1a** with 9-BBN provided the diastereomeric alcohol **2f** in ≥98% de. The alcohols **2c,d** were obtained only as mixtures which could be separated by preparative TLC. Alcohol **2d** could best be prepared by the 9-BBN reduction of ketone **1b**; a 93:7 diastereomer mixture was obtained. Synthesis of the alcohol **2c**, however, was particularly inefficient. Neither reaction of **1c** with methyllithium nor reduction of **1b** with sodium borohydride provided a **2c/2d** ratio more favorable than 70:30.

Experimental Section

General. Thin-layer chromatography (TLC) was carried out on 0.25-mm analytical and 1.00-mm preparative silica gel GF plates (Analtech). ^{1}H NMR spectra were taken in $CDCl_3$ (TMS internal standard) on Bruker WP-250 and JEOL FX-90Q instruments, unless otherwise stated. Infrared (IR) spectra were recorded on a Perkin-Elmer 467 spectrometer. Mass spectra (MS) were recorded on a Finnegan 4023 GC-MS instrument. Procedures for the preparation of **1a**, **3a,b**, and **1c** have been previously described.[5,6] Reactions were worked up, unless otherwise stated, by drying the organic layer over anhydrous Na_2SO_4 (or $MgSO_4$) and concentrating at reduced pressure. THF and diethyl ether were distilled from sodium–benzophenone ketyl under nitrogen. Column chromatography was carried out on Baker Analyzed Reagent silica gel, 60–200 mesh. Cyclopentene was passed through a short alumina (Fisher neutral) column prior to use.

Synthesis of Dihydroisoxazole 1b. To an ice-cold dichloromethane (60 mL) solution of the dicyclohexylamine salt of nitroacetone[14] (6 g, 21.1 mmol. *Caution: the free nitro compound is explosive!*[15]) was added an 0.3 M ethereal solution of diazomethane (150 mL). After stirring for 1 h at 0–5 °C, the solvent and excess diazomethane were removed and the residue was dissolved in benzene (200 mL). (*E*)-Stilbene (11.4 g, 63.3 mmol) and *p*-toluenesulfonic acid monohydride (9 g, 47.4 mmol) were then added and the mixture refluxed for 1 h. After cooling, the resulting solution was washed (two 50-mL portions of 5% NaOH), dried, filtered, and concentrated. The crude product was column chromatographed (CCl_4 followed by CH_2Cl_2 elution) to give stilbene followed by 1.74 g (31%) yield) of **1b**. Recrystallization from pentane gave an analytical sample: mp 54.5–55.5 °C; IR (melt) 1693 cm^{-1} (C=O); NMR δ 7.16–7.31 (m, 10 H), 5.60 (d, 1 H, *J* = 5.7 Hz), 4.50 (d, 1 H, *J* = 5.7 Hz), 2.46 (s, 3 H).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found: C, 76.79; H, 5.36.

Reaction of Dihydroisoxazole 1a with Methyllithium. To a cold (−78 °C) solution of **1a** (0.10 g, 0.31 mmol) in THF (10 mL) under N_2 was added in one portion methyllithium (0.61 mL of a 1.5 M solution in diethyl ether, 0.92 mmol). The mixture was stirred for 15 min after which water–THF (5 mL, 1:1) was added. After allowing the mixture to warm to room temperature, water (10 mL) and CH_2Cl_2 (30 mL) were added and the reaction was worked up. Preparative TLC afforded a 94% yield of alcohols **2a** and **2b** in a 99.5:0.5 ratio (HPLC[16], confirmed by NMR). Recrystallization (twice from hexanes–benzene) gave an analytical sample of **2a** as colorless cubes: mp 114.5–115 °C; IR (KBr) 3340 cm^{-1} (OH); NMR δ 6.98–7.36 (m, 15 H), 5.48 (d, 1 H, *J* = 5.8 Hz), 4.18 (d, 1 H, *J* = 5.8 Hz), 2.92 (s, 1 H), 1.64 (s, 3 H).

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.52; H, 6.15; N, 4.05.

Reaction of Dihydroisoxazole 1a with Methylmagnesium Bromide. Methylmagnesium bromide (0.27 mL of a 2.8 M solution in diethyl ether, 0.75 mmol) was added over 30 s to a cold (−78 °C) solution of **1a** (0.10 g, 0.31 mmol) in CH_2Cl_2 (10 mL) and the resulting solution was stirred for 30 min. Water (1 mL) and 1% HCl (3 mL) were then added and the reaction was worked up. Preparative TLC (25:75 EtOAc – hexanes) of the crude product gave a 72% yield of **2b** containing a trace of **2a** (98:2 ratio: HPLC,[16] confirmed by NMR). Recrystallization from hexanes–benzene gave an analytical sample of **2b** as coloress needles: mp 94.5–95 °C; IR (KBr pellet) 3340 cm^{-1} (OH); NMR δ 7.08–7.42 (m, 15 H), 5.44 (d, 1 H, *J* = 5.1 Hz), 3.98 (d, 1 H, *J* = 5.1 Hz), 1.82 [s, 4 H, (*CH*$_3$ and O*H*)]. Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16. Found: C, 80.50; H, 6.07.

Using THF, a 55% yield of alcohols **2b** and **2a** (80:20 ratio by NMR) was obtained.

Reaction of Dihydroisoxazole 1b with Phenyllithium. Phenyllithium (1.5 mL of a 2.4 M solution in diethyl ether, 3.4 mmol) was added dropwise over 30 s to a cold THF (20 mL, −78 °C) solution of **1b** (0.3 g, 1.13 mmol) under N_2 and the resulting solution was stirred for 15 min. Water–THF (10 mL, 1:1) was then carefully added at −78 °C, and the mixture allowed to warm to room temperature. Most of the tetrahydrofuran was evaporated and the residue was worked up. Preparative TLC (hexanes–ethyl acetate, 85:15) gave 0.32 g (82% yield) of **2b** and **2a** in a 99:1 ratio (HPLC,[16] confirmed by NMR). NMR and IR data showed the major product to be identical with that obtained from the reaction of **1a** with methylmagnesium bromide.

Reaction of Dihydroisoxazole 1b with Phenylmagnesium Bromide. Phenylmagnesium bromide (0.75 mL of a 3 M solution in diethyl ether, 2.26 mmol) was added dropwise over 30 s to a cold CH_2Cl_2 solution (10 mL, −78 °C) of **1b** (0.30 g, 1.13 mmol) under N_2 and the resulting mixture stirred for 30 min. Water (10 mL) was carefully added and the mixture allowed to warm to room temperature. The reaction was worked up to give crude product. Preparative TLC ($CH_{2c}l_2$ or 15:85 EtOAc – hexanes) gave an 82% yield of solid product containing **2a** and **2b** (≥99:1 HPLC,[16] confirmed by NMR).

Using diethyl ether at 0–5 °C, a 98:2 ratio (NMR) of **2a** and **2b** was obtained.

Reaction of Dihydroisoxazole 3a with Methyllithium. Methyllithium (2.4 mL of a 1.7 M solution in diethyl ether, 4.08 mmol) was added all at once to a solution of **3a** (0.086 g, 0.40 mmol) in THF (8 mL) at −78 °C. After stirring for 20 min, water (5 mL) was carefully added, and the mixture allowed to warm to room temperature. Saturated aqueous KCl (5 mL), 1% HCl (5 mL), and CH_2Cl_2 (20 mL) were then added and the reaction was worked up. Preparative TLC (25:75 ethyl acetate–hexanes) of the crude product gave solid material (0.081 g, 88% yield) containing diastereomers **4a** and **5a** in a 95:5 ratio (HPLC,[16] confirmed by NMR). Recrystallization from hexanes–benzene gave an analytical sample of **4a** as colorless needles: mp 76–77 °C; IR (melt) 3440 cm^{-1} (OH); NMR δ 7.25–7.57 (m, 5 H), 4.93–5.04 (m, 1 H), 3.62–3.87 (m, 1 H), 2.87 (br s, 1 H), 1.20–2.06 (m overlapping s at 1.86, total 9 H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41. Found: C, 72.82; H, 7.18.

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(16) We thank Dr. J. P. McCauley (Drexel University) for performing the HPLC analyses.

Reaction of Dihydroisoxazole 3a with Methylmagnesium Bromide. To a cold (−78 °C) solution of **3a** (0.050 g, 0.23 mmol) in CH_2Cl_2 (5 mL) under N_2 was added all at once methylmagnesium bromide (0.22 mL of a 3.2 M solution in diethyl ether, 0.69 mmol). The resulting solution was stirred for 30 min and was quenched with water (5 mL). After warming to room temperature, 1% HCl (5 mL) was added and the organic layer further worked up. Preparative TLC (25:75 ethyl acetate–hexanes) afforded a solid product containing diastereomers **4a** and **5a** (78% yield) in a 7:93 ratio. Recrystallization from hexanes–benzene gave an analytical sample of **5a**: mp 79.0–79.5 °C; IR (melt) 3440 cm^{-1} (OH); NMR δ 7.23–7.54 (m, 5 H), 4.94–5.02 (m, 1 H), 3.18–3.34 (m, 1 H), 2.63 (br s, 1 H), 1.23–2.00 (m overlapping s at 1.84, total 9 H).

Reaction of Dihydroisoxazole 3b with Methylmagnesium Bromide. To a cold (−78 °C) solution of **3b** (0.12 g, 0.47 mmol) in CH_2Cl_2 (5 mL) under N_2 was added dropwise over 5 min methylmagnesium bromide (1.2 mL of a 2.9 M solution in diethyl ether, 3.5 mmol), and the resulting solution was stirred for 20 min. The reaction was quenched with water (1 mL) and then 1% HCl (10 mL) was added, the layers were separated, and the organic layer was worked up. Preparative TLC (30:70 ethyl acetate–hexanes) of the crude residue gave 52 mg (42% yield) of **5b**[5] as the more mobile component: ^1H NMR δ 7.26–7.44 (m, 10 H), 5.58 (dd, 1 H, J = 9.1, 10.2 Hz), 3.21 (dd, 1 H, J = 10.2, 18 Hz) overlapping 2.97 (dd, 1 H, J = 9.1, 18 Hz), 2.75 (s, 1 H), 1.87 (s, 3 H).

Also obtained was 51 mg (41% yield) of **4b**[5] as the less mobile component: ^1H NMR δ 7.24–7.53 (m, 10 H), 5.54 (dd, 1 H, J = 8.6 and 10.8 Hz), 3.41 (dd, 1 H, J = 10.8 and 17.1 Hz), 2.93 (s, 1 H), 2.67 (dd, 1 H, J = 8.6 and 17.1 Hz), 1.88 (s, 3 H).

Reaction of Aldehyde 1c with Methyllithium. To a cold (−78 °C) solution of **1c** (0.050 g, 0.20 mmol) in THF (5 mL) under N_2 was added methyllithium (0.36 mL of a 1.4 M ethereal solution, 0.50 mmol), and the resulting solution was stirred for 20 min. Water (1 mL) and 5% HCl (5 mL) were added, and the reaction was worked up. Preparative TLC (20:80 ethyl acetate–hexanes) afforded in 76% yield an oil containing diastereomers **2c** and **2d** (70:30 ratio, NMR). A second preparative TLC (20:80 ethyl acetate–hexanes) separated the diastereomers and afforded an analytical sample of **2c**: NMR δ 7.18–7.42 (m, 10 H), 5.50 (d, 1 H, J = 6.4 Hz), 4.55 (q, 1 H, J = 6.8 Hz), 4.34 (d, 1 H, J = 6.4 Hz), 2.54 (br s, 1 H), 1.19 (d, 3 H, J = 6.8 Hz). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.00; H, 6.21.

Also obtained was an analytical sample of **2d**: NMR δ 7.18–7.44 (m, 10 H), 5.48 (d, 1 H, J = 6.4 Hz), 4.41 (d, J = 6.4 Hz superimposed on q, 2 H total), 1.94 (br s, 1 H), 1.38 (d, 3 H, J = 6.5 Hz); MS m/e 267 (M^+). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41. Found: C, 76.49; H, 6.48.

Reaction of Aldehyde 1c with Methylmagnesium Bromide. To a cold (−78 °C) solution of **1c** (0.050 g, 0.20 mmol) in CH_2Cl_2 (5 mL) under argon was added methylmagnesium bromide (0.10 mL of a 2.9 M etheral solution, 2.9 mmol). After stirring for 10 min, water (1 mL) was added, the mixture was allowed to warm to room temperature, and 5% HCl (5 mL) was added. Further workup afforded the crude products. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) gave a 95% yield of an oil containing **2c** and **2d** in a 1:2 ratio (NMR).

Reaction of Aldehyde 1c with Phenyllithium. To a cold (−78 °C) solution of **1c** (0.070 g, 0.28 mmol) in CH_2Cl_2 (7 mL) under argon was added phenyllithium (0.42 mL of a 2 M ethereal solution, 0.84 mmol). After stirring for 1 h, water (1 mL) was added, the reaction mixture allowed to warm to room temperature, and 5% HCl (5 mL) added. Further workup afforded the crude products. Preparative TLC (20:80 EtOAc–hexanes) gave a 70% yield of an oil containing **2e** and **2f** in a 90:10 ratio (NMR). A second preparative TLC (99:1 CH_2Cl_2–CH_3OH) gave a sample of **2e** which matched the sample obtained from reduction of **1a** using $NaBH_4$.

Reaction of Aldehyde 1c with Phenylmagnesium Bromide. To a cold (−78 °C) solution of **1c** (0.05 g, 0.20 mmol) in CH_2Cl_2 (5 mL) under argon was added phenylmagnesium bromide (0.15 mL of a 2 M ethereal solution, 0.30 mmol) and the resulting solution was stirred for 40 min. Water (1 mL) was added followed by 5% HCl (5 mL). Further workup afforded the crude products. Preparative TLC (20:80 EtOAc–hexanees) afforded an 86% yield of an oily mixture containing **2e** and **2f** in a 56:44 ratio (NMR).

Reduction of Dihydroisoxazole 1a with Sodium Borohydride. Sodium borohydride (0.069 g, 1.83 mmol) was added to an ethanolic (10 mL) solution of **1a** (0.052 g, 0.16 mmol), and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by adding water (5 mL), stirring 10 min, and then very slowly adding 5% HCl (5 mL). Further workup afforded the crude products, a 50:50 mixture of **2e** and **2f**. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) on baked (140 °C overnight) plates gave 0.026 g (50% yield) of **2e** as a viscous oil: NMR δ 7.03–7.41 (m, 15 H), 5.50 (d, 1 H, J = 7.0 Hz), 5.24 (d, 1 H, J = 4.6 Hz), 3.90 (d, 1 H, J = 7.0 Hz), 3.28 (d, 1 H, J = 4.6 Hz). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81. Found: C, 79.86; H, 5.97.

Also obtained by preparative TLC was 0.026 g (50% yield) of **2f** as a viscous oil: NMR δ 7.11–7.32 (m, 15 H), 5.55 (s, 1 H), 5.46 (d, 1 H, J = 6.1 Hz), 4.18 (d, 1 H, J = 6.1 Hz), 2.34 (br s, 1 H); MS m/e 329 (M^+). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81. Found: C, 79.84; H, 5.97.

Reduction of Dihydroisoxazole 1a with DIBAH. To a cold (−78 °C) solution of **1a** (0.08 g, 0.24 mmol) in toluene (5 mL) under N_2 was added DIBAH (1.22 mL of a 1 M solution in hexanes, 1.22 mmol) and the resulting solution was stirred for 90 min. Water (1 mL) was added to quench the reaction, followed at room temperature by 5% HCl (4 mL). After 15 min sitrring, further workup afforded the crude products. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) gave an 85% yield of an oil containing **2e** and **2f** in an 15:85 ratio (NMR).

Reduction of Dihydroisoxazole 1a with 9-BBN. To a cold (0–5 °C) solution of **1a** (0.06 g, 0.18 mmol) in THF (5 mL) under N_2 was added 9-BBN (0.5 M, 1.47 mL, 0.73 mmol) and the resulting solution was stirred for 4 h. Aqueous 3 M NaOH (4 mL) and 30% H_2O_2 (4 mL) were added and the resulting mixture was stirred for 2 days. Further workup and subsequent preparative TLC (99:1 CH_2Cl_2–CH_3OH) of the crude product gave 30 mg (50% yield) of **2f** with no detectable **2e** (NMR).

Reduction of Dihydroisoxazole 1a with K-Selectride. To a cold (0–5 °C) solution of **1a** (0.1 g, 0.31 mmol) in THF (7 mL) under argon was added K-Selectride (0.92 mL of a 1 M THF solution, 0.92 mmol) and the resulting solution was stirred for 1 h. Water–THF (2 mL, 1:1) was added followed by 3 M NaOH (2 mL) and 30% H_2O_2 (2 mL). The mixture was stirred for 10 min and was worked up. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) of the crude products gave 80 mg (79% yield) of **2f** and 11 mg (11% yield) of **2e** (88:12 ratio, confirmed by crude NMR).

Reduction of Dihydroisoxazole 1b with Sodium Borohydride. Sodium borohydride (0.189 g, 5 mmol) was added to a solution of **1b** (0.27 g, 1 mmol) in absolute ethanol (25 mL) under N_2 and the resulting solution was stirred for 1 h. The reaction was quenched with water (1 mL) and stirred for 10 min before 5% HCl (15 mL) was added. The resulting solution was worked up and the crude product purified by preparative TLC (99:1 CH_2Cl_2–CH_3OH) to give 24 mg (89% yield) of a mixture of **2d** and **2c** in a 1:2 ratio (NMR).

Reduction of Dihydroisoxazole 1b with L-Selectride. To a cold (−78 °C) solution of **1b** (0.1 g, 0.38 mmol) in THF (10 mL) under N_2 was added L-Selectride (0.76 mL of a 1 M THF solution, 0.76 mmol) and the resulting solution was stirred for 35 min. Water–THF (2 mL, 1:1) was added and the reaction mixture was allowed to warm to 0–5 °C. Then 3 M NaOH (2 mL) and 30% H_2O_2 (2 mL) were added and the mixture was stirred for 10 min. Further workup afforded the crude products. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) gave 91 7g (90% yield) of an oil containing **2d** and **2c** (55:45 ratio by NMR).

Reduction of Dihydroisoxazole 1b with K-Selectride. To a cold (−78 °C) solution of **1b** (0.1 g, 0.38 mmol) in THF (5 mL) under N_2 was added K-Selectride (0.60 mL of a 1 M THF solution, 0.60 mmol) and the resulting solution was stirred for 30 min. Water–THF (2 mL, 1:1) was added and the reaction mixture was allowed to warm to 0–5 °C. Then 3 M NaOH (2 mL) and 30% H_2O_2 (2 mL) were added and the mixture was stirred for 10 min. Further workup afforded the crude products. Preparative TLC (99 1 CH_2Cl_2–CH_3OH) gave 70 mg (70% yield) of an oil containing **2d** and **2c** (1:2 ratio by NMR).

Reduction of Dihydroisoxazole 1b with DIBAH. To a cold (−78 °C) solution of **1b** (0.07 g, 0.26 mmol) in toluene (5 mL) under

N_2 was added DIBAH (1.04 mL of a 1 M solution in hexanes, 1.04 mmol) and the resulting solution was stirred for 3 h. Water (2 mL) was added and the reaction mixture was stirred for 10 min followed by addition of 5% HCl (5 mL). Further workup afforded the crude products. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) gave 52 mg (74% yield) of an oil containing **2d** and **2c** (79:21 ratio by NMR).

Reduction of Dihydroisoxazole 1b with BH_3–THF. To a cold (0–5 °C) solution of **1b** (0.04 g, 0.15 mmol) in THF (4 mL) under N_2 was added borane in THF (0.9 mL of a 1 M solution) and the resulting solution was stirred for 4 h. Water–THF (2 mL, 1:1) was added followed by 1% HCl (2 mL). Further workup afforded the crude products. Preparative TLC (99:1 CH_2Cl_2–CH_3OH) gave 37 mg (95% yield) of an oil containing **2d** and **2c** (52:48 ratio by NMR).

Reduction of Dihydroisoxazole 1b with 9-BBN. To a cold (0–5 °C) solution of **1b** (0.04 g, 0.15 mmol) in THF (5 mL) under N_2 was added 9-BBN (3 mL of an 0.5 mM solution in THF, 1.5 mmol) and the resulting solution was stirred for 210 min at 0–5 °C and at ambient temperature for 1 h. Volatiles were removed at reduced pressure, benzene (2 mL) followed by ethanolamine (0.092 mL) were added, and the resulting solution was stirred overnight at room temperature. Dichloromethane (10 mL) was added and the mixture was filtered. The filtrate was worked up to afford crude product. Preparative TLC (20:80 EtOAc–hexanes) gave 36 mg (90% yield) of an oil containing **2d** and **2c** (93:7 ratio by NMR).

Conversion of Oxirane 7 to Alcohol 2c. To a cold (0–5 °C) solution of oxirane **7**[8] (0.02 g, 0.08 mmol) in THF (2 mL) under N_2 was added lithium triethylborohydride (0.20 mL of a 1 M solution in THF, 0.20 mmol) and the resulting solution was stirred for 15 min. Water–THF (1 mL, 1:1) was added and then 5% HCl (5 mL). Further workup afforded the crude products. Preparative TLC (35:625 EtOAc–hexanes) gave 14 mg (68% yield) of **2c** free of any isomeric **2d**.

Supplementary Material Available: Calculated bond lengths for **8** (s-trans and s-cis conformers), ^1H NMR spectrum of **5a**, ORTEP drawing of **2f**, crystal data for **2f**, tables of refined positional and thermal parameters for **2f**, and tables of bond lengths and bond angles for **2f** (7 pages). Ordering information is given on any current masthead page.

Studies in the Cyclopropabenzene Series: ^{13}C NMR Correlations for Alkylidenecyclopropabenzenes

Brian Halton,*,† Qi Lu,† and Peter J. Stang‡

Department of Chemistry, Victoria University of Wellington, P.O. Box 600, Wellington, New Zealand, and Department of Chemistry, The University of Utah, Salt Lake City, Utah 84112

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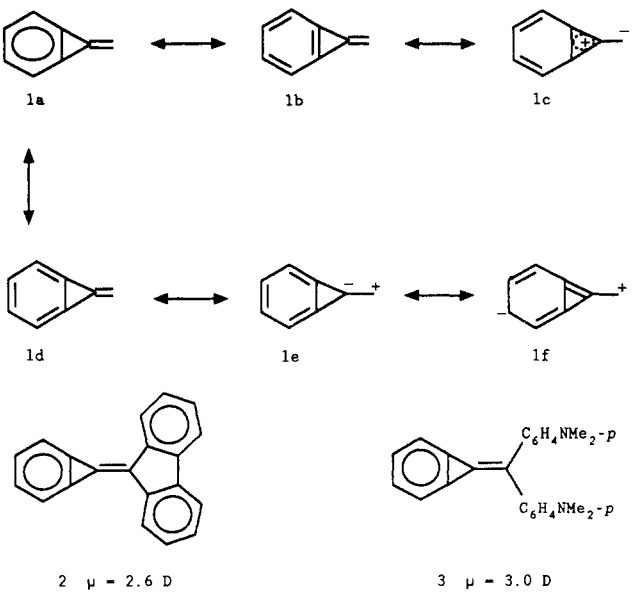
The ^{13}C NMR spectra of a series of (arylmethylene)- and (diarylmethylene)-1*H*-cyclopropa[*b*]naphthalenes, **6** and **8**, and -cyclopropabenzenes, **7** and **9**, have been analyzed. A systematic change in the ^{13}C chemical shifts of the cyclopropabenzenyl carbon atoms is induced by remote para substituents R which correlate linearly with the corresponding Hammett constant σ_p^+. Depending upon the nature of R the cyclopropabenzenyl unit accepts more or donates less π-electron density.

Since the first derivatives of methylenecyclopropabenzene (**1**) were reported[1] in 1984, many interesting physical[2,3] and chemical[4,5] properties of this novel series of hydrocarbons have emerged.[6] Not least among these is the ambiphilic character of the cyclopropabenzenyl component of **1** and the ability this has to stabilize both positive and negative charge as illustrated by the polar derivatives **2** and **3**, respectively.[7] Thus when substituted with electron-withdrawing groups at the exocyclic center, contributions to the structure from **1a–c** appear to dominate whereas with electron-donating substituents the alternative forms **1d–f** are important. In the singlet excited state these features are even more significant, and fluorescence with marked Stokes shifts and high quantum efficiency have been recorded.[8]

The range of alkylidenecyclopropabenzenes that is now available allows for the assignment of the ^{13}C NMR resonances of the cyclopropabenzenyl moiety and these are now reported. The effects of the substituents in the *p*-aryl derivatives **6a–f** and **7a,b** and the *p,p'*-diaryl derivatives **8a–e** and **9a–d** are felt in the cyclopropabenzenylidene unit and excellent correlations with the Hammett σ_p^+ constants are found.

Experimental Section

Compounds. The compounds studied were prepared from cyclopropabenzene (**4**) or cyclopropa[*b*]naphthalene (**5**) by silyl-Wittig olefination as previously reported.[1,3-9]



^{13}C NMR Spectra. The ^{13}C NMR spectra were recorded for $CDCl_3$ and DMSO-d_6 solutions (~10% solutions) where possible,

† Victoria University of Wellington.
‡ The University of Utah.

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