method (see the supplementary material) and was coupled to **4** under the influence of $Hg(CN)_2$–$HgBr_2$ to regio- and stereospecifically afford tetrasaccharide **6** in 56% yield.[15-17] This remarkable difference in the reactivities of the three hydroxyl groups in **4** is noteworthy since it allows rapid oligosaccharide construction without protecting groups (vide infra for a second application of this finding).[18] Acetylation of the remaining hydroxyl groups in **6** led to **7** (86%); subsequent photolytic cleavage of the *o*-nitrobenzyl ether led to lactol **8** (82%). Removal of the phenylthio group by Ph_3SnH–AIBN-initiated radical chemistry required heating to 130 °C and recycling, furnishing compound **9** (42% yield, plus 45% starting material for each cycle). Finally, treatment of **9** with DAST resulted in formation of the requisite fluoride **10** in 78% yield (ca. 4:1 ratio of β- and α-anomers).

Scheme III exhibits the continuation of the buildup toward S-diLe^x compound **2**. Thus, trisaccharide **3** was first converted to trihydroxyglycoside **11** by glycosylation (87% yield) followed by concomitant deacetylation–dephthaloylation using hydrazine and finally selective N-acetylation (83% over two steps). Again, by taking advantage of the reactivity differences between the three hydroxyl groups in **11**, the next glycosylation step (using the tetrasaccharide donor **10**) was successfully carried out without protection, leading to sialylated compound **12**[17] in 51% yield.[19] Generation of the carboxylic acid **13** from its methyl ester was best accomplished with lithium iodide in pyridine (120 °C, 80%, plus 17% recovered starting material); subsequent exposure to hydrazine at 80 °C removed both the phthalimido and the acetate groups, resulting in the formation of the amino acid **14**. Acetylation of **14** with excess acetic anhydride in methanol–methylene chloride furnished a mixture of polyhydroxy acid **15** and its δ-lactone **16** (ca. 1:1 ratio, 75% overall yield from **13**). Finally, debenzylation of **15** by hydrogenolysis proceeded smoothly to produce the targeted compound **2** in 95% yield. Lactone **17** was also debenzylated by catalytic hydrogenolysis to afford the corresponding polyhydroxylated lactone (95% yield), which was found to open up quantitatively to the target oligosaccharide **2** on standing in D_2O (NMR tube, 2 h, 25 °C).

The described chemistry renders S-diLe^x and its derivatives such as **2** readily available in pure form for extensive biological investigations. Further studies envisioned in this field may expand the library of biological tools and provide therapeutic agents in the area of inflammation and related conditions.

Acknowledgment. We express our many thanks to Drs. Dee Huang and Gary Siuzdak of The Scripps Research Institute for their excellent NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health and The Scripps Research Institute.

Supplementary Material Available: Schemes for the synthesis of compounds **3** and **5** and listings of selected physical data for compounds **4**, **6**, **9**, **11**, **12**, **16**, and **2** (11 pages). Ordering information is given on any current masthead page.

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(15) For similar couplings, see: Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835.

(16) The stereochemistry of the newly generated glycoside bond in **6** was tentatively assigned on mechanistic considerations and was confirmed by the observation of a doublet in the gated proton-decoupled ^{13}C NMR spectrum of **9** (125 MHz, $CDCl_3$, δ 168.5, $J_{C-1S.A.,H-3axS.A.} = 5.5$ Hz); see: Hori, H.; Nakajimia, T.; Nishida, Y.; Ohru, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317.

(17) The regiochemistry of the coupling reaction to give **6** was proven by ^1H NMR analysis of the corresponding bis(acetate) **7**, which exhibited the expected large downfield chemical shifts for the galactose C-2 and C-4 protons [(500 MHz, $CDCl_3$) **6**: C-2, δ 3.36; C-4, 4.04. **7**: C-2, δ 5.07; C-4, 5.46]; similar observations were made for **12**. The bis(acetate) of **12** exhibited two new downfield peaks in the ^1H NMR spectrum corresponding to the newly acetylated 2 and 4 positions of galactose [(500 MHz, benzene-d_6) bis(acetate) of **12**: C-2′, δ 5.19; C-4′, 5.68]. The pre-existing acetylated C-2‴ and C-4‴ positions exhibited similar downfield chemical shifts [(500 MHz, benzene-d_6) **12**: C-2‴, δ 5.47; C-4‴ δ 5.81. bis(acetate) of **12**: C-2‴ δ 5.49; C-4‴ δ 5.80].

(18) Paulsen, H.; Paal, M. *Carbohydr. Res.* **1985**, *137*, 39.

(19) From the two anomeric fluorides of **10**, only the β-anomer reacted, the α-anomer being recovered unchanged. The yield of 51% was based on consumed triol **11**.

Direct Observation of the Formation and Rearrangement of Carbene/Allyl Sulfide Ylides

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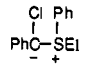
More than 25 years ago, Parham and Groen reported that dichlorocarbene reacted with acyclic allylic sulfides to form sulfonium ylides that subsequently underwent "allylic rearrangement" (Scheme I).[1] In current terminology, the ylide would be said to undergo a [2,3] sigmatropic rearrangement.[2] Now, we have used laser flash photolysis (LFP) to probe the closely related reactions of phenylchlorocarbene (PhCCl) and phenylfluorocarbene (PhCF) with phenyl allyl sulfide, methyl allyl sulfide, and γ,γ-dimethylallyl methyl sulfide. We describe here the first direct observational and absolute kinetic studies of both the formation and rearrangement of the intermediate carbene/allyl sulfide ylides.

LFP-generated carbenes react with thiophene and thioanisole to give spectroscopically observable *S*-ylides.[3] Similarly, we find that LFP[4] of phenylchlorodiazirine[5] in PhSEt–pentane affords absorptions at 280–340 and 380–450 nm, λ_{max} 310 and 420 nm. These absorptions are stable for >10 μs, are not observed in the absence of sulfide,[6,7] and are attributed to ylide **1**. Appropriately, the appearance of **1**, monitored at 420 nm, is first-order in [sulfide], with $k_f = (2.9 \pm 0.2) \times 10^9\ M^{-1}\ s^{-1}$.

LFP of phenylchloro- and phenylfluorodiazirine[8] gave PhCCl[7] and PhCF,[9] respectively, which were readily captured by allylic sulfides **2a–c** in pentane or isooctane solutions to afford the transient ylides **3a–c** (from PhCCl) and **4a–c** (from PhCF). The ylides exhibited absorptions analogous to those of **1** but, in contrast to **1**, ylides **3** and **4** were unstable. Their decay made it difficult to directly assess k_f for their formation, but this could be accomplished using the pyridine probe method.[3]



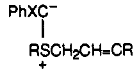
$PhC^{-}(Cl)$–$S^{+}(Ph)Et$

1

$RSCH_2CH{=}CR_2'$

2

a, R=Ph, R′=H
b, R=Me, R′=H
c, R=R′=Me



$PhXC^{-}$–$RS^{+}CH_2CH{=}CR_2'$

3, X=Cl ⎰ a-c as
4, X=F ⎱ in 2

Thus, LFP-generated PhCCl reacted with 8×10^{-4} M pyridine in pentane to afford the known pyridinium ylide.[3] The first-order rate constant for the appearance of this ylide (monitored at 480 nm, where the *S*-ylides do not absorb), plotted against (e.g.) the concentration of $(1-9) \times 10^{-4}$ M added sulfide **2a**, gave a linear correlation whose slope ($2.3 \times 10^9\ M^{-1}\ s^{-1}$) was taken as k_f for the formation of *S*-ylide **3a**.[10] Rate constants for the formation of *S*-ylides **3** and **4** from reactions of PhCCl and PhCF with

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(1) (a) Parham, W. E.; Groen, S. H. *J. Org. Chem.* **1964**, *29*, 2214. (b) Parham, W. E.; Groen, S. H. *Ibid.* **1965**, *30*, 728. (c) Parham, W. E.; Groen, S. H. *Ibid.* **1966**, *31*, 1694.

(2) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 956 f.

(3) Jackson, J. E.; Soundararajan, N.; Platz, M. S.; Liu, M. T. H. *J. Am. Chem. Soc.* **1988**, *110*, 5595.

(4) The LFP conditions were 351 nm, 50–80 mJ, 14 ns. For a description of our apparatus, see: Moss, R. A.; Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G.; Wlostowska, J.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341.

(5) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(6) PhCCl also has λ_{max} 310 nm (isooctane), but it decays on the microsecond time scale.[7] The reaction of PhCF with PhSEt is analogous to that of PhCCl.

(7) Turro, N. J.; Butcher, J. A., Jr.; Moss, R. A.; Guo, W.; Munjal, R. C.; Fedorynski, M. *J. Am. Chem. Soc.* **1980**, *102*, 7576.

(8) Cox, D. P.; Moss, R. A.; Terpinski, J. *J. Am. Chem. Soc.* **1983**, *105*, 6513.

(9) Cox, D. P.; Gould, I. R.; Hacker, N. P.; Moss, R. A.; Turro, N. J. *Tetrahedron Lett.* **1983**, *24*, 5313.

(10) This value is similar to $k_f = 2.9 \times 10^9\ M^{-1}\ s^{-1}$ for the formation of **1** from PhCCl and PhSEt; see above.

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Scheme I

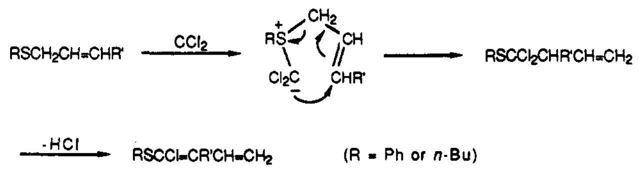


Table I. Kinetics of Ylide Formation and Disappearance[a]

carbene	sulfide	ylide	$10^{-9}k_f$ (M^{-1} s^{-1})[b]	$10^{-6}K_d$ (s^{-1})[c]
PhCCl	**2a**	**3a**	2.3 ± 0.1	12.5 ± 0.5[d]
PhCCl	**2b**	**3b**	4.9 ± 0.2	10 ± 1
PhCCl	**2c**	**3c**[e]	1.8 ± 0.1	5.2 ± 0.3
PhCF	**2a**	**4a**	1.8 ± 0.2	1.7 ± 0.1
PhCF	**2b**	**4b**	4.8 ± 0.5	4.3 ± 0.2
PhCF	**2c**	**4c**	2.1 ± 0.2	2.4 ± 0.1

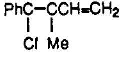
[a] By LFP[4] in pentane or isooctane solution at 20 °C. [b] Bimolecular rate constant for carbene/sulfide ylide formation, determined in competition with pyridine ylide formation,[3] monitored at 480 nm, [pyridine] = 8×10^{-4} M. [c] First-order rate constant for ylide decay, monitored at 310 nm. [d] An identical rate constant was obtained by monitoring ylide decay at 420 nm. [e] See also structure **7**.

sulfides **2a–c** are all determined in this way; they are collected in Table I.

The decay and rearrangement of ylides **3** and **4** were also examined. Consider, as illustrative, ylide **3a** from PhCCl and sulfide **2a**. LFP generation of PhCCl in 0.011 M **2a** gave ylide **3a**, λ_{max} 310 and 420 nm. The latter absorbance exhibited growth–decay kinetics, consistent with the formation and rearrangement (see below) of **3a**. At 310 nm, we observed non-first-order decay, with the complexity caused by the quenching of PhCCl (formed within the laser pulse[6]) superimposed on the transient absorbance of ylide **3a**. However, at high [sulfide], the PhCCl was quenched so rapidly that *only* the first-order decays of the ylide absorptions were seen at either 310 or 420 nm.[11] Moreover, kinetic analysis furnished identical rate constants, k_d = $(1.2 \pm 0.1) \times 10^7$ s^{-1}, for the decay of **3a** at either wavelength. Importantly, k_d is *independent* of [sulfide] (0.23–0.54 M), so that the rate constant does indeed reflect the first-order disappearance of the ylide. LFP rate constants for the decay of *S*-ylides **3a–c** and **4a–c** (from PhCF) are all similarly determined at [**2a–c**] = 0.09–0.54 M; values of k_d appear in Table I.

The products of these carbene/allyl sulfide reactions were most readily studied with the more volatile methyl allyl sulfides, **2b** and **2c**, which could be more easily removed after reaction than sulfide **2a**.[12] Thus, steady-state irradiation (200-W, focused Osram XE UV lamp, λ > 340 nm) of phenylchlorodiazirine (A_{372} = 1.5) in 0.20 M **2b**–pentane at 20 °C gave >80%[13] of (*E*)- and (*Z*)-1-phenyl-1-(methylthio)-1,3-butadiene (**5**). The structure assignments derive from NMR[14] and GC–MS data (M^+ are *m*/*e* 176, both isomers). The parallel reaction of PhCF with **2b** also led to *Z*/*E*-**5** in 90% yield. A similar reaction of PhCCl with γ,γ-dimethylallyl methyl sulfide (**2c**) gave a near quantitative mixture of **6**, the [2,3] sigmatropic rearrangement product of the initially formed ylide **3c** (**7**), and ketone **8**, the hydrolysis product of **6**.

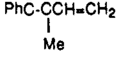
5


$\mathrm{PhC(SMe)(Cl){-}C(Me)_2CH{=}CH_2}$

6


$\mathrm{PhClC^{-}{-}\overset{+}{S}(Me)CH_2CH{=}CMe_2}$

7 (= 3c)


$\mathrm{PhC(=O){-}C(Me)_2CH{=}CH_2}$

8

Product characterization was again based on NMR[15] and GC–MS data (M^+ analysis). Attempted purification of **6** on silica gel led to its complete conversion to **8**. The reaction of PhCF with sulfide **2c** followed a course analogous to that of PhCCl.

Clearly, PhCCl and PhCF react with allylic sulfides in a manner parallel to that of CCl_2 (Scheme I).[1] We observe sigmatropic rearrangement of **7** to **6** in the reaction of PhCCl with **2c** and, most importantly, LFP permits us to visualize the formation and decay of the *S*-ylide intermediates in this and related reactions. Table I reveals that, with each substrate, $k_f > 10^9$ M^{-1} s^{-1}. Obviously, the S atom is a voracious carbene trap, far superior to the vinyl groups of these allylic sulfides. Mono- to trisubstituted alkenes react with PhCCl or PhCF with $k \simeq (0.9–1.3) \times 10^8$ M^{-1} s^{-1},[16] so that we would not expect cyclopropanation to effectively compete with ylide formation from substrates **2**, nor have we observed any cyclopropane products.

The ylides derived from PhCCl (**3a–c**) decay 2–7 times faster than the corresponding ylides (**4a–c**) formed from PhCF (Table I), possibly because enhanced inductive stabilization by F (vs Cl) at the ylides' carbanionic centers slows down the [2,3] rearrangements of the F-substituted ylides. We also observe a modest 2-fold deceleration in the decay of ylides derived from substrate **2c** vs those formed from **2b**. This may be ascribed to the increased steric hindrance to rearrangement offered by the γ-methyl substituents of **2c**.

The present direct observational studies lend strong support to the product-based mechanistic proposals of Parham (Scheme I).[1] The LFP methodology can also be applied to assess solvent effects and activation parameters for these and related carbene ylide reactions.

Acknowledgment. We are grateful to the National Science Foundation for financial support.

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(11) We calculate that the pseudo-first-order formation of ylide **3a** at [**2a**] = 0.23 M would be $0.23 \times k_f = 0.23 \times 2.3 \times 10^9 = 5.3 \times 10^8$ s^{-1}, more than 10 times faster than the observed decay of **3a**.

(12) LFP absorbances and kinetic phenomena were entirely analogous for the reactions of PhCCl or PhCF with all three substrates, **2a–c**.

(13) In the presence of excess of K_2CO_3 to neutralize liberated HCl, the yield of **5** exceeded 95%. The isomer ratio was 4:1–7:1 by GC or NMR, respectively.

(14) Major isomer: (200 MHz, δ, $CDCl_3$) 2.22 (s, 3 H, SMe), 4.90–5.22 (m, 2 H, $=CH_2$), 6.15–6.40 (m, 2 H, =CHCH=), 7.34 ("s", 5 H, Ph). The minor isomer (~14%) had δ 1.99 (SMe).

(15) ^{1}H NMR data of **6** (δ, $CDCl_3$): 1.22, 1.24 (2s, 6 H, Me_2C), 1.97 (s, 3 H, SMe), 4.9–5.1 (m, 2 H, $=CH_2$), 6.05–6.20 (m, 1 H, CH=), 7.2–7.4 + 7.7–7.8 (m's, Ph). ^{1}H NMR data of **8** (δ, $CDCl_3$): 1.40 (s, 6 H, Me_2C), 5.17–5.27 (m, 2 H, $=CH_2$), 6.11–6.26 (m, 1 H, CH=), 7.3–7.5 + 7.8–7.9 (m's, 5 H, Ph); IR (**8**) 1670 cm^{-1} (C=O); M^+, 174.

(16) Moss, R. A.; Turro, N. J. In *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum: New York, 1990; pp 213 f.

Stepwise Transannular Bond Formation between the Bridgehead Atoms in $ZP(MeNCH_2CH_2)_3N$ Systems

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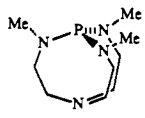
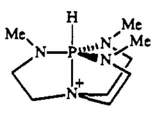
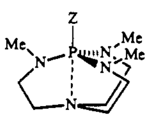
We have recently described the extraordinary Lewis basicity of the phosphorus in **1** for protons to produce the unexpectedly weak conjugate acid **2**.[1–7] The transannulation process that



1



2



	Z
3	*trans*-$Cl_2Pt(1)$[6]
4	S[6]
5	S_2C[6]
6	*cis*-$Br(OC)_4Re$
7	Cl_2Hg
8	$MeS(S)C^+$
9	$PhN{=}C^+{\cdot}SMe$

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(1) Lensink, C.; Xi, S.-K.; Daniels, L. M.; Verkade, J. G. *J. Am. Chem. Soc.* **1989**, *111*, 3478.

(2) Schmidt, H.; Lensink, C.; Xi, S.-K.; Verkade, J. G. *Anorg. Allg. Chem.* **1989**, *578*, 75.

(3) Schmidt, H.; Xi, S.-K.; Lensink, C.; Verkade, J. G. *Phosphorus, Sulfur Silicon* **1990**, *49/50*, 163.

(4) Laramay, M. A. H.; Verkade, J. G. *J. Am. Chem. Soc.* **1990**, *112*, 9421.

(5) Laramay, M. A. H.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163.

(6) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1990**, *29*, 2214.

0002-7863/92/1514-3129$03.00/0