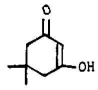
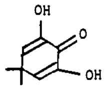
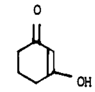
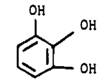
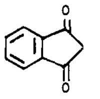
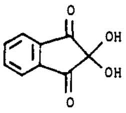
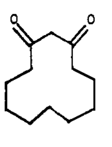
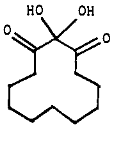
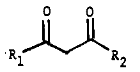
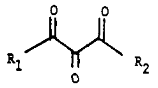
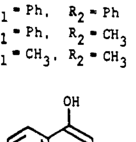
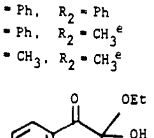
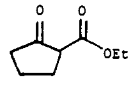
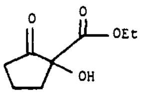
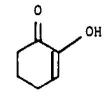
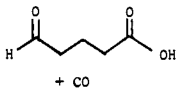
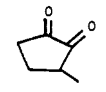
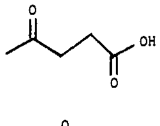
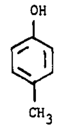
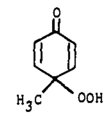
J. Am. Chem. Soc. **1982**, *104*, 4696-4698

Table I

dicarbonyl substrate	product[b]	yield with F^-	results, absence of F^-
		72%, 1½ h	a
		70%, 2 h	a
		75%, 3 h	b
		60%, 1 h	b
			
R_1 = Ph, R_2 = Ph	R_1 = Ph, R_2 = Ph	97%, 2 h	b
R_1 = Ph, R_2 = CH_3	R_1 = Ph, R_2 = CH_3[e]	72%, 3 h	b
R_1 = CH_3, R_2 = CH_3	R_1 = CH_3, R_2 = CH_3[e]	66%, 2½ h	b
		70%, ½ h	b
		49%, 2 h (2 equiv. F^-)	b
		65%, 3 h	c
		72%, 5 h	c
		87%, 3 h	a

[a] The reaction was very slow and yielded an intractable mixture of product. [b] There was no detectable oxygen uptake or change in TLC behavior after several hours of irradiation. [c] A very slow reaction, accompanied by severe dye bleaching. [d] Satisfactory NMR, IR, and elemental analyses were obtained for all new compounds. [e] Isolated as the addition product with *o*-phenylenediamine.

be further converted to 2 mol of III by reaction with $^1O_2$.

The α-diketone–singlet oxygen reaction also appears to take place by initial hydroperoxide formation. In the cases studied, these hydroperoxides undergo cyclization and cleavage as shown in Scheme II to yield aldehydo or keto acids along with carbon monoxide. Similar behavior has been observed in the photooxidation of flavones and coumaranones.[7a,b] In the absence of fluoride ion, the reaction was sluggish and severe dye bleaching occurred.

As noted in Table I, all of the compounds that were studied underwent photooxidation very slowly or not at all in the absence of fluoride ion. Tetraalkylammonium bromides and chlorides were not effective in accelerating the reaction. Potassium fluoride in the presence of 18-crown-6 does promote the photooxidations although a full equivalent of the crown ether is necessary for rapid reaction. When tetrabutylammonium hydroxide was used in place of the fluoride, uptake of oxygen took place at approximately the same rate, but complex mixtures of products were obtained as a result of base-catalyzed condensations and competing reactions of triplet oxygen in the alkaline medium.

We are giving further study to the role of fluoride ion in promoting these photooxidations and to the use of these tricarbonyl intermediates in synthesis. Clark and Miller[8,11] have proposed that the fluoride ion effect observed in the alkylation and condensation reactions of enols is associated with hydrogen-bonding phenomena leading to increased electron density on the enol oxygen. We believe that similar phenomena are responsible for the striking fluoride ion effect observed in the reactions of enols with singlet oxygen.

Acknowledgment. This work was supported by NIH Grant GM-13854. The support of the NSF/NMR Northeast Regional Facility at Yale University (Grant CHE-7916210) is acknowledged.

Registry No. I, 126-81-8; II, 81003-49-8; III, 32999-99-8; 2,6-dihydroxy-4,4-dimethyl-2,5-cyclohexadien-1-one, 78102-66-6; 3-hydroxy-2-cyclohexen-1-one, 30182-67-3; 1,2,3-benzenetriol, 87-66-1; 1*H*-indene-1,3(2*H*)-dione, 606-23-5; 2,2-dihydroxy-1*H*-indene-1,3(2*H*)-dione, 485-47-2; 1,3-cyclododecanedione, 6498-49-3; 2,2-dihydroxy-1,3-cyclododecanedione, 82415-36-9; 1,3-diphenyl-1,3-propanedione, 120-46-7; diphenylpropanetrione, 643-75-4; 1-phenyl-1,3-butanedione, 93-91-4; 1-phenyl-1,2,3-butanetrione, 4435-51-2; 2,4-pentanedione, 123-54-6; 2,3,4-pentanetrione, 921-11-9; 4-hydroxy-2*H*-1-benzopyran-2-one, 1076-38-6; 3-ethoxy-3-hydroxy-3,4-dihydro-2*H*-1-benzopyran-2,4-dione, 82415-37-0; ethyl 2-oxocyclopentanecarboxylate, 611-10-9; ethyl 1-hydroxy-2-oxocyclopentanecarboxylate, 82415-38-1; 2-hydroxy-2-cyclohexen-1-one, 10316-66-2; 5-oxopentanoic acid, 5746-02-1; 3-methyl-1,2-cyclopentanedione, 765-70-8; 4-oxopentanoic acid, 123-76-2; 4-methylphenol, 106-44-5; 4-hydroperoxy-4-methyl-2,5-cyclohexadien-1-one, 57749-82-3; tetrabutylammonium fluoride, 429-41-4.

Chemistry of Higher Order, Mixed Organocuprates. 4.[1] Stereochemical Outcome of Substitution Reactions at Unactivated Secondary Centers Using Organocopper Reagents

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Santa Barbara, California 93106

Received May 19, 1982

Earlier reports[1,3] from these laboratories have demonstrated that the simple yet subtle shift from copper halide based organocuprates (i.e., R_2CuLi (**1**)) to copper cyanide derived species leads to a new class of highly reactive yet thermally stable[4] reagents of general formula $R_2Cu(CN)Li_2$ (**2**). These copper complexes react readily with α,β-unsaturated ketones in a Michael fashion[1]

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[1] Part 3. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron Lett.*, in press.

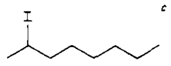
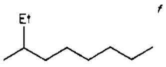
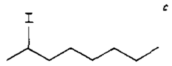
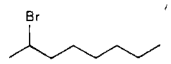
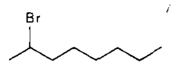
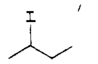
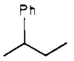
[2] Recipient of an American Cancer Society Junior Faculty Research Award, 1981–1983.

[3] (a) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305. (b) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *Ibid.* **1981**, *103*, 7672.

[4] Bertz, S. H., Bell Laboratories, private communication. "Abstracts of Papers", 183rd National Meeting, of the American Chemical Society, Las Vegas, NV, March, 1982; American Chemical Society: Washington, D.C., 1982; ORGN 110.

0002-7863/82/1504-4696$01.25/0

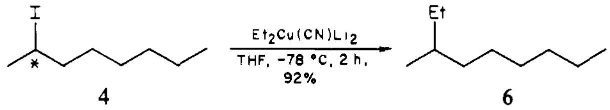
Table I. Reactions of Organocuprates with Optically Active Bromides and Iodides in THF

entry	substrate	$[\alpha]_D$, deg[a]	cuprate	product	yield, %[b]	specific $[\alpha]_D$, deg[a]	corr $[\alpha]_D$, deg	inversion, %
A	 [c]	−42.82 (−50.98)[d]	$Et_2Cu(CN)Li_2$[e]	 [f] **6**	92	−0.10[g]	−0.11	1.1–1.2[h]
B	 [c]	−42.26 (−50.31)[d]	Et_2CuLi	**6**	82	0.00[g]	0.00	0
C	 [i]	+35.42 (+35.78)[j]	$Et(Me)Cu(CN)Li_2$[k]	**6**	72	+8.32	+9.60	97–103[h]
D	 [i]	+35.58 (+35.94)[j]	Et(Me)CuLI	**6**	59	+8.29	+9.53	97–102[h]
E	 [l]	+31.98 (+36.98)[m]	Ph_2CuLi		60[n]	−0.74	−0.88	3.2[o]

[a] Rotation taken at 19 °C unless stated otherwise. [b] By quantitative VPC using *tert*-butylcyclohexane as an internal standard. [c] Alcohol precursor had $[\alpha]^{22}_D$ +8.31° (84% ee). [d] Corrected value based on 84% ee for 2-octanol. [e] For the preparation of this reagent see ref 3c. [f] Confirmed by comparison with an authentic sample. [g] Rotation recorded at 22 °C. [h] Range due to reported values for 3-methylnonane (9.30–9.86 °C). See ref 9. [i] Alcohol precursor had $[\alpha]^{19}_D$ −9.83° (99% ee). [j] Corrected value based on 99% ee for 2-octanol. [k] For the preparation of these reagents, see ref 1. [l] Alcohol precursor had $[\alpha]^{19}_D$ −12.79° (92% ee). [m] Corrected value based on 92% ee for 2-butanol. [n] By quantitative VPC using xylene as internal standard; ca. 10% starting material was recovered. [o] Based on lit. value of $[\alpha]^{20}_D$ +27.3°; Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

and also effect substitution reactions, cleanly delivering ligands of various types to open epoxides[3a] and displacing halogen (bromides, iodides) at secondary unactivated centers.[3b] This latter coupling is particularly noteworthy in view of numerous reports claiming that Gilman reagents (i.e., **1**) lead predominantly to products of reduction and/or elimination.[5] In order to extend the utility of this discovery for purposes of devising synthetic schemes, we felt it incumbent upon us to elucidate the stereochemical consequences of ligand transfer from copper to carbon. Herein we describe the first general study on the stereochemical outcome of the substitution process with *both* lower and higher order cuprates.

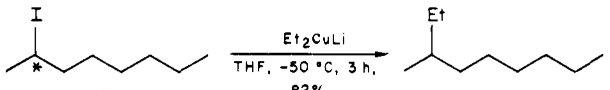
It was anticipated at the outset that treatment of an optically active secondary bromide or iodide with **2** would give the product corresponding to inversion at carbon. A previous study showed that the reaction of Ph_2CuLi (**3**) with (*R*)-(−)-2-bromobutane led to (*S*)-(+)-2-phenylbutane, suggesting 84–92% inversion.[6] It is implied in this observation that secondary halides in general would react in a similar manner, and hence (*R*)-(−)-2-iodooctane (**4**) was chosen as substrate and prepared from commercially available (*S*)-(+)-2-octanol[7] (PI_3/CS_2).[8] The higher order cuprate derived from EtLi (i.e., $Et_2Cu(CN)Li_2$ (**5**) was selected as reagent since the expected chiral product, 3-methylnonane (**6**), is known,[9] and any coupling between the two ethyl ligands would generate only butane as byproduct thus simplifying isolation of the desired hydrocarbon. In the event, treatment of **4** with **5** (eq 1) led to the product in 92% (VPC) yield. Workup and isolation by preparatory VPC[10] afforded essentially *racemic* **6**.[11,12] These results are summarized in Table I.



(1)

4 $[\alpha]^{22}_D$ −50.98° **6** $[\alpha]^{22}_D$ −0.11°

Although we were initially dismayed by this finding, it was not obvious why the stereochemical outcome using CuCN-based reagents should be different from that of lower order cuprates, **1**.[6] Therefore, the same experiment was conducted with **4** and Et_2CuLi (eq 2). Once again, racemic **6** was obtained![13,14]



(2)

4 $[\alpha]^{22}_D$ −50.31° **6** $[\alpha]^{22}_D$ −0.00°

This somewhat satisfying result was still not secure without examining the reactions of the corresponding bromides. While literature precedent[6] pointed to an inversion process (vide supra),

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(5) For representative examples, see: Posner, G. H. *Org. React.* **1975**, *22*, 253.

(6) Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

(7) *S*-(+)-2-Octanol was purchased from Fluka ($[\alpha]^{22}_D$ +8.31°) while (*R*)-(−)-2-octanol is available from Aldrich ($[\alpha]^{19}_D$ −9.83°). The maximum reported specific rotation is $[\alpha]^{17}_D$ +9.9° (neat) ("Handbook of Chemistry and Physics"; CRC Press: Cleveland, OH.

(8) Coulson, E. J.; Gerrard, W.; Hudson, H. R. *J. Chem. Soc.* (*London*) **1965**, 2364. The maximum reported observed rotation for 2-iodooctane is α^{20}_D 64.63°. This corresponds to $[\alpha]^{20}_D$ = 48.96° with a density of 1.32 at 20 °C as listed in the Handbook of Chemistry and Physics;[7] that for the bromide is α^{20}_D 44.91° and implies a $[\alpha]^{20}_D$ 40.83° with a density of 1.10.

(9) The highest known experimental value prior to this work for the specific rotation of **6** is $[\alpha]^{25}_D$ 9.30°: Letsinger, R. L.; Traynham, J. G. *J. Am. Chem. Soc.* **1950**, *72*, 849. Extrapolated values have also been reported: $[M]^{25}_D$ 13.7–14.0°, which corresponds to a specific rotation of $[\alpha]^{25}_D$ = 9.65–9.86°: Lardicci, L.; Botteghi, C.; Benedetti, E. *J. Org. Chem.* **1966**, *31*, 1534.

(10) With a 2-m column of 10% Apiezon N on Chromosorb W (60/80 mesh) at 70 °C.

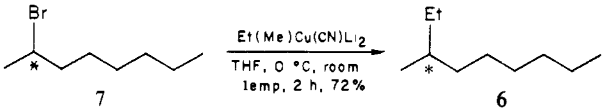
(11) Hydrocarbon of >99% purity (by VPC).

(12) In a separate experiment, **4** was treated with **5** (1 equiv) at −78 °C for 5 min and quenched. The iodide was recovered by distillation (97% pure by VPC) and had a rotation of $[\alpha]^{19}_D$ 44.72° (*c* 34, $CHCl_3$) which compares with $[\alpha]^{19}_D$ 46.16° (*c* 34, $CHCl_3$) by using a standard solution of the same starting iodide. This result indicates that racemization of the starting material does not occur under these reaction conditions. Approximately 50% of the starting material was consumed in this reaction.

(13) Isolated by preparatory VPC and analyzed to be 90% pure. The lower purity of **6** is due to the presence of octane formed here in greater quantities than with $Et_2Cu(CN)Li_2$ by the reduction of the iodide. Being dissatisfied with this level of purity, we again separated the material by preparatory VPC and now found it to be >99% pure. The rotation was retaken in solution (some was lost during collection) ($[\alpha]^{19}_D$ 0.00° (*c* 2.8, $CHCl_3$)) and compared with a standard solution of **6** ($[\alpha]^{19}_D$ 7.75° (*c* 2.8, $CHCl_3$), observed; $[\alpha]^{19}_D$ 9.81° (*c* 2.8, $CHCl_3$), corrected).

(14) A recent report on the reaction of lithium dihydroanthracenyl cuprate with (+)-2-iodooctane states that substitution occurs with inversion of configuration at carbon: Hebert, E. *Tetrahedron Lett.* **1982**, *23*, 415. Dr. Hebert informs us that although the yield in the reaction is low (20%), the product 9-(2-octyl)-9,10-dihydroanthracene has been isolated with 54% ee, which corresponds to 68–70% inversion. This result would appear to be contrary to our findings.

the use of an aromatic cuprate (i.e., **3**) under most atypical conditions[15] suggested that *alkyl*lithium-derived organocuprates should be investigated. Thus, reaction of (*S*)-(+)-2-bromooctane (**7**)[16] with Et(Me)Cu(CN)Li_2[17] at 0 °C to room temperature (eq 3) afforded (72%) optically active **6**[18] with a rotation clearly indicative of a net Walden inversion having taken place.[9]

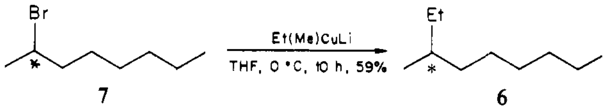


(3)

7 $[\alpha]^{19}{}_D$ +35.78°

6 $[\alpha]^{19}{}_D$ +9.60°

Similarly, treatment of **7** with the lower order counterpart Et(Me)CuLi[19] gave (*S*)-(+)-**6**[18] with essentially the same rotation (eq 4).

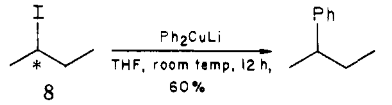


(4)

7 $[\alpha]^{19}{}_D$ +35.94°

6 $[\alpha]^{19}{}_D$ −9.53°

These experiments serve to establish that the mechanism of the coupling process at carbon is substrate and not reagent dependent. To further lend credence to this work, we prepared (*S*)-(+)-2-iodobutane (**8**)[20] and treated it with Ph_2CuLi (eq 5). Whereas the corresponding bromide goes with inversion,[6] essentially *racemic* *sec*-butylbenzene was isolated by preparatory VPC,[21] in line with the data presented above.[22]



(5)

8 $[\alpha]^{19}{}_D$ +36.98°

$[\alpha]^{19}{}_D$ −0.88°

Finally, some of the implications of this study should be brought to light as they may have a considerable impact on organocopper chemistry. These include the following: (1) it has been shown that the nature of the halide undergoing displacement appears to determine the stereochemistry of the resulting carbon center. Thus, where complete stereocontrol is required, bromides are the preferred substrates.[23] (2) With proper control of experimental parameters, Gilman cuprates, in many cases, will effect substitution chemistry in synthetically useful yields.[24] (3) The substitution process at *primary* centers is also likely to be dependent upon the leaving moiety. This is strongly suggested by the observation that treatment of primary iodide **9** with **2**, R = *n*-Bu at −100 °C, for 30 min afforded 20–30% of the reduction product (eq 6).[25]

$$\underset{\mathbf{9}}{n\text{-}C_7H_{15}I} \xrightarrow[\text{THF, -100 °C, 30 min}]{(n\text{-Bu})_2\text{Cu(CN)Li}_2} \underset{50\%}{n\text{-}C_{11}H_{24}} + \underset{30\%}{n\text{-}C_7H_{16}} + \underset{20\%}{\text{SM}}$$

Acknowledgment. Financial support from the National Institutes of Health (GM 28128), the American Cancer Society (JFRA No. 37, B.H.L.), and the Committee on Research, UCSB, Sigma Xi, is gratefully acknowledged.

Registry No. 1 (R = Et), 38297-20-0; **2** (R = Bu), 80473-69-4; **3**, 23402-69-9; (*R*)-**4**, 29117-48-4; **5**, 80473-71-8; (±)-**6**, 82373-57-7; (*S*)-**6**, 53213-47-1; (*S*)-**7**, 1191-24-8; (*S*)-**8**, 29882-56-2; **9**, 4282-40-0; Et(Me)Cu(CN)Li_2, 82352-24-7; Et(Me)CuLi, 82352-23-6; (±)-*sec*-butylbenzene, 135-98-8; undecane, 1120-21-4; heptane, 142-82-5.

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[15] This displacement was performed at 51 °C for 72 h.

[16] Formed from (−)-2-octanol with PBr_3 (neat); cf ref 8.

[17] It was necessary to switch to the still more highly mixed cuprate since use of **5** led to a considerable amount of competing reduction under a variety of conditions. The selectivity of transfer (ethyl/methyl) was ca. 12:1.

[18] Isolated by preparatory VPC with purity of >99% (by VPC).

[19] As in ref 17, Et_2CuLi gave low yields (~18%) of 6.

[20] Goodwin, D. G.; Hudson, H. R. *J. Chem. Soc. B* **1968**, 1333. In this work, 2-iodobutane is prepared from PI_3/CS_2 and shows $\alpha^{20}{}_D$ 60.4° or $[\alpha]^{20}{}_D$ 37.99° with a density of 1.59 as listed in the CRC Handbook of Chemistry and Physics.[7]

[21] With a 3-m column of 4% SE-30 on Chromosorb P (60/80 mesh). The purity of *sec*-butylbenzene isolated was determined to be >99% (by VPC).

[22] In view of the coupling between an aryl ligand in **3** and a secondary iodide (**8**), it is apparent that there is *some* dependence of the reaction on the cuprate involved since $Ph_2Cu(CN)Li_2$ reacts with 2-iodooctane affording only trace amounts of the desired product.[3b]

[23] Tosylates are also known to react with inversion: Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.

[24] In addition to the examples shown in the text, we have also found that *n*-Bu_2CuLi reacts with iodocyclohexane at −50 °C in ~1 h to afford *n*-butylcyclohexane in quantitative yield; cf.: Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1968**, *90*, 5615.

[25] We have from this observation gone on to show that primary bromides are functionally equivalent (in terms of leaving-group ability) to iodides by switching from reagents **1** to **2**. Hence, e.g., 5-bromovaleronitrile reacts with *n*-$Bu_2Cu(CN)Li_2$ (1.3 equiv) at −50 °C (2.5 h) to afford pelargononitrile in 92% isolated yield (Kozlowski, J.; Parker, D., unpublished work). A general study will be reported in due course. Typically, considerably higher temperatures (ca. 0 °C) are required with Gilman reagents.[5]

6-Methyl-1,6-diazabicyclo[6.2.2]dodecane: An Inside, Outside Six-Atom Bridged Boat Piperidine

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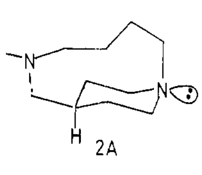
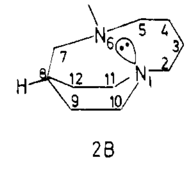
Received February 1, 1982

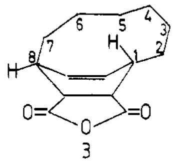
2-Methyl-1,2-diazabicyclo[2.2.2]octane **1**[1] was bis-alkylated with 1,4-diiodobutane in two steps, following the methodology of Alder and co-workers[2] to give hexaalkylhydrazine dication $\mathbf{2}^{2+}$,[3] which was reduced to the neutral diamine **2**[4] (see Scheme I). Two classes of conformations are available for **2** depending on the configuration at the piperidine nitrogen N_1, the chair piperidine class 2A (in which the piperidine ring could reverse) and the boat piperidine class **2B**, which is the inside, outside isomer of 6-methyl-1,6-diazabicyclo[6.2.2]dodecane. Gassman and Hoye[5] recently described the X-ray structure of the substituted (i,o)-bicyclo[6.2.2]dodecane **3**, which is a very strained compound, as evidenced by the large bond-angle deformations found for its 6-bridge. The nitrogen at position 1 of **2B** replaces the inner C_1H bond of **3** with a sterically less demanding nitrogen lone pair, which should reduce the strain in **2B** relative to **3**, and N_1 of **2B** can also flatten more easily to further relieve strain in **2B** relative to **3**.



2A



2B



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[1] Prepared from 1,2-diazabicyclo[2.2.2]octane (Nelsen, S. F.; Gannett, P. M.; Steffek, D. J. *J. Org. Chem.* **1980**, *45*, 3857) by formaldehyde/cyanoborohydride reductive methylation (Nelsen, S. F.; Weisman, G. R. *Tetrahedron Lett.* **1973**, 2321).

[2] (a) Alder, R. W.; Goode, N. C.; King, T. J.; Mellor, J. M.; Miller, B. W. *J. Chem. Soc., Chem. Commun.* **1976**, 173. (b) Alder, R. W.; Gill, R.; Goode, N. C. *Ibid.* **1976**, 973. (c) Alder, R. W.; Sessions, R. B.; Mellor, J. M.; Rawlins, M. G. *Ibid.* **1977**, 747. (d) Alder, R. W.; Sessions, R. B. *J. Am. Chem. Soc.* **1979**, *101*, 3651. (e) Alder, R. W.; Sessions, R. B.; Bennet, A. J.; Moss, R. E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 603. (f) For a review of the special properties of diamines, see: Alder, R. W.; Sessions, R. B. "The Chemistry of Functional Groups; Supplement F: The Chemistry of Amines, Nitroso, and Nitro Compounds"; Patai, S., Ed.; Wiley: New York, 1982; Chapter 18, p 763.

[3] $\mathbf{2}^{2+}(BF_4^-)_2$ (dec 244–245 °C) gave a satisfactory combustion analysis and reasonable spectral data.

[4] **2** (mp 54–56 °C (sealed tube)) gave a high-resolution MS mass of 187.1783, an acceptable deviation of 0.1 ppm from $C_{11}H_{22}N_2$.

[5] Gassman, P. G.; Hoye, R. C. *J. Am. Chem. Soc.* **1981**, *103*, 215.

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