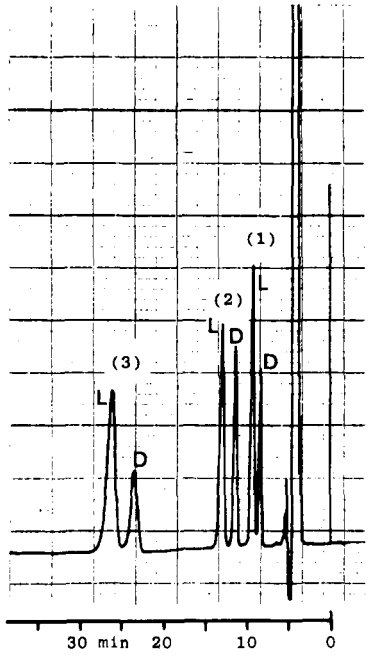

Figure 1. Chromatographic optical resolution of the enantiomeric mixtures of (1) *N*-acetyl-*O*-*tert*-butylserine *tert*-butyl ester, (2) *N*-acetylleucine *tert*-butyl ester, and (3) *N,O*-diacetyltyrosine *tert*-butyl ester. The chromatographic conditions were as described in Table I legend. Mobile phase: 4% (v/v) 2-PrOH in *n*-hexane. A mixture of three pairs of D- and L-amino acid derivatives, each consisting of an enriched concentration of the L enantiomers, was injected onto the FVA column.

stationary surface and L isomers to be more stable. The FVA column was insensitive to the proline derivatives (separation 18) because of the absence of the NH group. Studies on CPK and Büchi's molecular models showed slight conformational differences in diastereomeric associations. In spite of the clear distinction in the association energy of hydrogen bonding and that provided by other stronger and more specific complexations such as host–guest and metal–chelate complexations, the new method has at least as much separation power as previous ones.

The method is based on highly efficient chromatographic technology with nonaqueous phase operation. Through this technology, it has been possible to maximize the number of theoretical plates. Thus, by employing microparticulate packing material and optimizing the solvent systems,[12-14] direct separation of the enantiomers of amino acid derivatives has become feasible. Because of its normal phase operation, prepartive scale separations can be accomplished readily so that the method may be satisfactorily applied to peptide syntheses with high optical purities which is demanded for biologically active substances and drugs.

These results will be useful in the analyses of D-amino acids and D-element-containing peptides which have been found in some microorganisms and are thought to also exist in higher animals.[15] Many families of naturally occurring chiral products containing proton-releasing or proton-accepting groups are of interest on designing chiral stationary phases with minimized recognition powers as well as a maximum number of theoretical plates.

(12) Hara, S. *J. Chromatogr.* **1977**, *137*, 41.
(13) Hara, S.; Fujii, Y.; Hirasawa, M.; Miyamoto, S. *J. Chromatogr.* **1979**, *149*, 143.
(14) Hara, S.; Hirasawa, M.; Miyamoto, S.; Ohsawa, A. *J. Chromatogr.* **1979**, *169*, 117.
(15) Masters, P. M.; Bada, J. L.; Zigler, J. S., Jr. *Nature (London)* **1977**, *269*, 71.

Akira Dobashi, Kitaro Oka, Shoji Hara*

Tokyo College of Pharmacy
Horinouchi, Hachioji, Tokyo 192-3, Japan

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Direct Evidence for Ketocarbene–Ketocarbene Interconversion

Sir:

In contrast to the impressive histories of carbonium ion, carbanion, and free-radical rearrangements, the carbene–carbene rearrangement[1] was recorded less than 15 years ago with the report of Shechter's group.[2] Not until 1968 was ketocarbene–ketocarbene rearrangement[3] shown to occur in decomposition of α-diazo ketones, presumably via oxirene by a series of studies of Strausz's group.[4] Interest in this rearrangement has intensified in recent years since the oxirenes, considered[5] a potential 4π antiaromatic system, have been of theoretical and synthetic importance. Nevertheless, only indirect evidence has just been provided for the ketocarbene rearrangement by some sensitive chemical probes, i.e., photochemical decomposition of isotopically labeled α-diazo ketones[4,6] and the thermal and photochemical decompositions of asymmetrically substituted α-diazo ketones,[7] in spite of the fact that the rearranged carbene has been trapped chemically in most of the other systems reported, e.g., aromatic carbene–arylcarbene rearrangement.[1] Moreover, little information exists as to the exact nature of the rearrangement, e.g., the roles of multiplicities and electronic excitation, effects of structure on the relative stability of ketocarbenes in equilibrium, etc. A study is now reported of photochemical processes of three pairs of asymmetrically substituted α-diazo ketones[8] (**1** and **2**) in methanol

$$\underset{\underset{N_2}{\|}}{\text{PhCCOR}} \xrightarrow[-N_2]{h\nu} \underset{\mathbf{3}}{\text{PhC}\ddot{\text{C}}\text{OR}} \rightleftharpoons \underset{\mathbf{4}}{\text{PhCO}\ddot{\text{C}}\text{R}} \xrightarrow[-N_2]{h\nu} \underset{\underset{N_2}{\|}}{\text{PhCOCR}}$$

1 **2**

a, R = Me; b, R = Et; c, R = i-Pr

which reveals that (i) the isomeric singlet ketocarbenes (**3** and **4**) from **1** and **2** are actually in equilibrium, (ii) fractional populations are highly dependent upon the substituents on carbenic carbon, and (iii) the rearranged ketocarbene is trapped intermolecularly for the first time.

Direct irradiation of α-diazopropiophenone (**1a**) in degassed methanol through Pyrex filter gave the ester **5** arising from the Wolff rearrangement (WR) product and the OH insertion product **6**. Surprisingly, similar irradiation of positionally isomeric diazo ketone (**2a**) also resulted in the formation of the same reaction

$$\mathbf{1}\text{ or }\mathbf{2} \xrightarrow[\text{MeOH}]{h\nu} \underset{\mathbf{5}}{\text{PhCHRCO}_2\text{Me}} + \underset{\mathbf{6}}{\text{PhCH(OMe)COR}} + \underset{\mathbf{7}}{\text{PhCOCH}{=}\text{CR}_1\text{R}_2}$$

a, R = Me, $R_1 = R_2$ = H; **b**, R = Et, R_1 = H, R_2 = Me; **c**, R = *i*-Pr, $R_1 = R_2$ = Me

products (**5** and **6**) in similar yields (Table I). Interestingly, products expected from carbene **4a**, e.g., OH insertion product or vinyl ketone **7a**, were not detected in the reaction mixture. In

(1) See, for review: Jones, W. M. *Acc. Chem. Res.* **1977**, *10*, 353–359.
(2) Vander Stouw, G. G. *Diss. Abstr.* **1965**, *25*, 6974. For a complete report of this work, see: Vander Stouw, G. G.; Kraska, A. R.; Shechter, H. *J. Am. Chem. Soc.* **1972**, *94*, 1655–1661.
(3) See, for review: Meier, H.; Zeller, K. P. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32–43.
(4) (a) Csizmadia, I. G.; Gont, J.; Strausz, O. P. *J. Am. Chem. Soc.* **1968**, *90*, 7360–7361. (b) Thornton, D. E.; Gosavi, R. G.; Strausz, O. P. *Ibid.* **1970**, *92*, 1768–1769. (c) Frater, G.; Strausz, O. P. *Ibid.* **1970**, *92*, 6654–6656. (d) Fenwick, J.; Frater, G.; Ogi, K.; Strausz, O. P. *Ibid.* **1973**, *95*, 124–132. (e) Csizmadia, I. G.; Gunning, H. E.; Gosavi, R. K.; Strausz, O. P. *Ibid.* **1973**, *95*, 133–137.
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(7) (a) Matlin, S. A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2623–2630. (b) Cormier, R. A.; Freeman, K. M.; Schnur, D. M. *Tetrahedron Lett.* **1977**, 2231–2234. (c) Timm, U.; Zeller, K.-P.; Meier, H. *Chem. Ber.* **1978**, *111*, 1549–1557.
(8) Diazo ketones **1**[8a] and **2**[8b] were prepared according to the procedure of Regitz and purified by recrystallization just before use. All diazo ketones showed satisfactory spectroscopic data. (a) Regitz, M. *Chem. Ber.* **1965**, *98*, 1210–1225. (b) Regitz, M.; Menz, F. *Ibid.* **1968**, *101*, 2622–2632.

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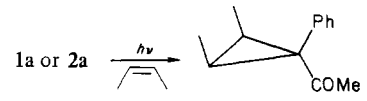
Table I. Product Distributions in the Photolysis[a] of 1 and 2 in Methanol

diazo ketones	direct (D) or sensitized (S)[c]	yields, %[b] 5	6	7
1a	D	50.0	35.0	*d*
	S	18.7	47.5	*d*
2a	D	52.9	39.1	*d*
	S	17.6	53.6	*d*
1b	D	51.3	12.5	5.1
2b	D	46.6	12.1	9.9
	S	28.3	15.1	17.6
1c	D	36.1	1.4	26.6
2c	D	38.7	2.3	28.2
	S	25.1	5.9	32.5

[a] Irradiations were performed on a 25 mM solution of diazo ketones in degassed methanol at 20 °C through a Pyrex filter. All products were identified by GC comparisons with authentic samples and GC–mass spectral techniques. Other minor products detected in each experimental condition were methyl benzoate and double-hydrogen-abstraction products. The benzoate was formed in ~20% yield when irradiation was carried out in nondegassed methanol. [b] Yields were determined by GC and based on diazo ketones used. [c] Irradiated (>355 nm) in the presence of more than 10-fold excess of Ph_2CO so as to assure that >98% of the incident light was absorbed by the sensitizer. Sensitized decomposition of 1b and 1c was not attempted since these compounds have strong absorption at longer wavelength. [d] Trace.

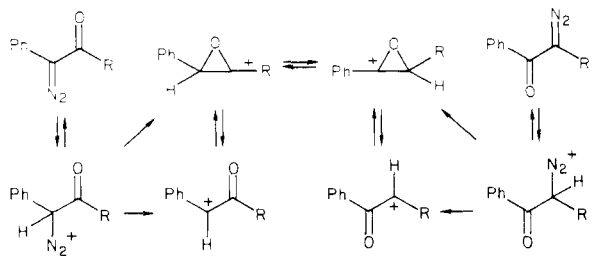
a marked contrast, direct photolysis of **2c** in methanol afforded appreciable amount of vinyl ketone **7c** along with the WR product **5c**, and only a small amount of OH insertion product **6c** was detected in this case. Isomeric diazo ketone **1c** also gave **7c** and **5c** in comparable yields upon irradiation at the expense of OH insertion product of **3c**. Similarly, the same reaction mixtures were obtained in the irradiation of either **1b** or **2b** (Table I).

Present data nicely verify the earlier suggestions[4-7] that isomeric α-ketocarbenes are in equilibrium or at least interconvert via oxygen migration. Possible involvement of carbonium ion[9] resulting from protonation of diazo ketones by methanol as an intermediate is removed by the findings that (1) the sensitized decompositions also lead to the rearrangement found in the direct photolyses (vide infra), (2) similar scrambling is observed in the irradiation of **1** and **2** in frozen methanol at −196 °C, where the proton-donor activities of alcohols are greatly depressed, and (3) acid-catalyzed decomposition of **1a** and **2a** in methanol in the dark resulted in the formation of **6a** and 2-methoxypropiophenone (OH insertion product from carbene **4a**), respectively, showing no sign of scrambling in the product distributions. More convincing evidence for the intervention of free carbene was obtained by the trapping experiment with olefins. Thus, the irradiation of either **1a** or **2a** in *cis*-2-butene resulted in the formation of the same reaction mixtures, in which the cyclopropane (**8**) formed from carbene **3a** was the major product.[10]



8

(9) A referee has suggested a reasonable mechanism for the interconversion of the positional isomer using carbonium ion:



Formation of **4** and **8** in the photolysis of **2** provides the first direct evidence that free carbene is indeed involved in the ketocarbene rearrangement. Moreover, the results clearly indicate the obvious effects of substituents on the carbene–carbene rearrangement. The extent of oxirene participation in the photodecomposition of α-diazo ketones has been frequently estimated[4,6] by means of labeling studies in the WR, viz., isotopic analysis of scrambled ^{13}C over both carbon atoms of the ketene generated. There has been accumulating evidence,[11] however, that supports Kaplan and Meloy's mechanism[12] in which the photochemical WR takes place directly through the excited singlet state of the conformational isomer, i.e., s-*Z*, whereas that of the s-*E* isomer eliminates nitrogen to form a ketocarbene leading to characteristic carbenic products and/or ketene. The previous technique[4,6] focusing only on the WR product, then, might pose some ambiguity on a free carbene–carbene rearrangement, or, at least, less accurately represent the extent of the rearrangement especially in direct photolysis. In order to clarify these problems and get a deeper insight into the mechanism of oxygen migration, we next examined the effect of sensitizer on the photolysis of **1** and **2** (Table I). As can be seen from the data, sensitization caused marked decrease in the yield of WR product concomitant with increase in other carbenic products (**6** and **7**). Interestingly, characteristic products of triplet carbene, e.g., double-hydrogen abstraction product, were not formed appreciably although the sensitizer absorbed >98% of incident light under these conditions. Since the sensitization circumvents[13] the formation of singlet excited state of diazo ketones, as is evident from the marked reduction in the WR, these results clearly eliminate either the precursor diazo ketone or ketene[14] as a possible intermediate for oxygen migration. Dominant formation of **6** and **7**, characteristic products from singlet carbene[15] even in the sensitized decomposition, while initially shocking, is easily interpreted as indicating that rapid intersystem crossing of the initially formed triplet carbene to the singlet is significant and its rate is substantially greater than the overall rate of the triplet reactions, as has been frequently observed[11a,d,13] in other similar carbene systems. The results provide strong experimental evidence for the involvement of free singlet ketocarbene in the rearrangement.[16]

The origin of the effect of alkyl substituents on the fractional populations of isomeric carbenes (**3** and **4**) is quite interesting. Almost complete scrambling in the product distributions in the photolytic mixtures from isomeric diazo ketones indicates that the activation energy for the rearrangement is much lower than those for the reactions from each carbene. The observed effect of R on the product distributions might reflect on the stability of carbene. It is somewhat surprising, however, to note that, in going from methyl to isopropyl groups, the stability effect of the alkyl group becomes comparable or superior to that of the phenyl group. An alternative and more probable explanation is that the product distributions might reflect the changes in the activation energy differences for the carbenic reactions. For example, the activation energy for H migration might be reduced in going from methyl to isopropyl as has been predicted[17] for $C^{\delta+}$--$H^{\delta-}$ polari-

(10) NMR analysis showed the near-exclusive formation of the syn isomer **8**, in which the phenyl group is located cis to the methyl groups. Similar predominance (>90%) of the syn isomer formation has been noted in the addition of phenylcarboethoxycarbene with *cis*-2-butene: Creary, X. *J. Am. Chem. Soc.* **1980**, *102*, 1611–1618.

(11) (a) Tomioka, H.; Kitagawa, H.; Izawa, Y. *J. Org. Chem.* **1979**, *44*, 3072–3075. (b) Roth, H. D.; Manion, M. L. *J. Am. Chem. Soc.* **1976**, *98*, 3392–3393. (c) Kaplan, F.; Mitchell, M. L. *Tetrahedron Lett.* **1979**, 759–762. (d) Tomioka, H.; Okuno, H.; Izawa, Y., *J. Org. Chem.*, in press.

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(13) (a) Roth, H. D.; Manion, M. L. *J. Am. Chem. Soc.* **1975**, *97*, 779–783. (b) Roth, H. D. *Acc. Chem. Res.* **1977**, *10*, 85–91.

(14) Russell, R. L.; Rowland, F. S. *J. Am. Chem. Soc.* **1970**, *92*, 7508–7510.

(15) See, for example: Moss, R. A., Jones, M., Eds. "Carbenes"; Wiley: New York, 1973, 1975, Vol. I, II.

(16) It has been indicated[4e,7a] indirectly that triplet ketocarbenes do not rearrange via oxirene intermediate since sensitization greatly reduced the formation of enones from rearranged ketocarbene and the percent of scrambling in ketone. Singlet carbene is shown[1] to be involved in the aromatic carbene–arylcarbene rearrangement.

zation of the bond being broken in the transition state, whereas that for OH insertion from **3** is apparently not affected by remote group R.

Finally, we have not detected trapped products of oxirene, i.e., methoxyoxiranes, in the present reaction system, although these products were not unduly reactive under these conditions of photolysis. This supports the recent calculations[18] which predict the lifetime of oxirene is too short to be trapped chemically.

(17) Su, D. T. T.; Thornton, E. R. *J. Am. Chem. Soc.* **1978**, *100*, 1872–1875.
(18) Strausz, O. P.; Gosavi, R. K.; Denes, A. S.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1976**, *98*, 4784–4786.

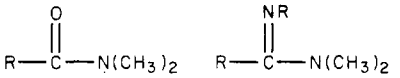
Hideo Tomioka,* Hiroshi Okuno, Shingo Kondo, Yasuji Izawa
Department of Industrial Chemistry
Faculty of Engineering
Mie University, Tsu, Mie 514, Japan
Received April 29, 1980

α-Substitution of Amines via Dipole Stabilized Carbanions from Formamidines

Sir:

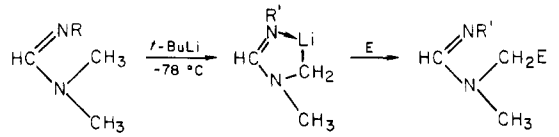
Deprotonation and alkylation of the α carbon of amines has been effected in various ways which involve the use of a masked amino function.[1-3] Prominent among these methods is the use of *N*-nitroso amines[4] and *N,N*-dimethylamides.[5] However, the potential carcinogenicity of the former and the steric bulk required in the latter render these approaches to alkylated amines less than desirable.

N,N-Dimethyl amidines **2** may be considered synthetically equivalent to *N,N*-dimethyl amides **1**. In contrast to amides,



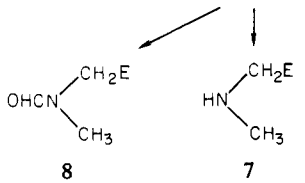
1 **2**

amidines have not been explored with respect to their reaction with strong bases.[6] We now report that amidines may serve as a generally useful precursor to α-substituted amines by metalation of **3**, **4**, or **5** to the dipole-stabilized carbanion, **6**, and treatment



3, R = cyclohexyl
4, R = *n*-Bu
5, R = *t*-Bu

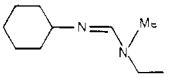
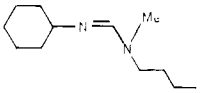
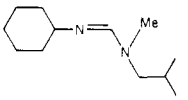
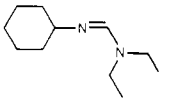
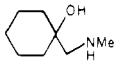
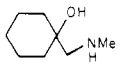
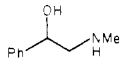
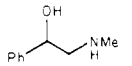
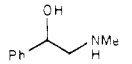
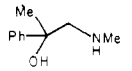
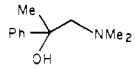
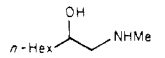
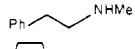
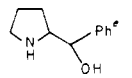
6



8 **7**

with various electrophiles, E. Hydrolysis provides the elaborated amines **7** or the *N*-formyl derivative **8** in good yield (Table I). In this preliminary report, pyrrolidine was also effectively alkylated via its amidine derivative (Table I, entry 14). The formamidines **3–5** as well as that derived from pyrrolidine **9** were prepared from *N,N*-dimethylformamide and *N*-formylpyrrolidine,[7] respectively, in 75–85% overall yield.[8,9]

Table I. α-Substituted Amines from Metalation of Formamidines

entry	amidine	electrophile	product	yield, %[a]
1	3	MeI		85
2	3	*n*-PrI		82
3	3	*i*-PrI		*b*
4	3	MeI (twice)		88
5	3	cyclohexanone		45[c]
6	5	cyclohexanone		40[c]
7	3	PhCHO		77[c]
8	4	PhCHO		71[c]
9	5	PhCHO		76[c]
10	3	$PhCOCH_3$		64[c]
11	3	$PhCOCH_3$		67[d]
12	3	*n*-HexCHO		40[c]
13	4	$PhCH_2Br$		54[f]
14	9	PhCHO		57[c]

[a] Yields are based on purified products and have not been optimized. [b] The crude product is a 2:1 mixture of starting material and alkylated product. [c] Product after hydrolysis of the corresponding formamidines. [d] Product after treating the *N*-formyl derivative with $LiAlH_4$. [e] Obtained as a 3:1 mixture of diastereomers. This ratio has the potential of increasing with a systematic survey of reaction conditions. [f] Hydrolyzed with $HCl-H_2O$–MeOH.

(1) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275 and references cited therein.
(2) Barton, D. H. R.; Lamotte, G.; Motherwell, W. B.; Narang, S. C. *J. Chem. Soc., Perkin Trans. 1.* **1979**, 2030.
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(8) Formamidines **3–5** and **9** were prepared by treating an ice-cold CH_2Cl_2 solution of the formamidinium salt (prepared from the *N*-formyl compound with 1.0 equiv of dimethyl sulfate with heating for 2 h at 60–90 °C under nitrogen) with 1.0 equiv of the primary amine and stirred at room temperature overnight. The reaction mixture was washed with 10% KOH and the CH_2Cl_2 solution, dried, evaporated, and distilled [**3**, bp 90–110 °C, (12 torr), colorless oil; **4**, bp 155–170 °C; **5**, bp 80–90 °C, (12 torr); **9**, bp 130–150 °C, (12 torr)]. All formamidines showed a singlet at δ 7.1–7.6 for the formyl proton.
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