species, react, at spin equilibrium, with the singlet carbene quencher methanol with about the same rate constant. The absolute rate constant of reaction of trifluoroethanol with diadamantylcarbene is (1.71 ± 0.32) × 10^8 M^{-1} s^{-1}. The trifluoroethanol rate constant was also found to be 1.51 × 10^8 M^{-1} s^{-1} by Stern–Volmer analysis in good agreement with the direct method. Triethylsilane reacts with carbene **2** with an absolute rate constant of (7.33 ± 2.2) × 10^6 M^{-1} s^{-1}. GC–MS analysis of this reaction mixture revealed the formation of diadamantylmethane and hexaethyldisilane as products which shows that it is **2T** rather than **2S** that reacts with triethylsilane.

In summary, oxygen trapping has been used to study the dynamics of a ground-state triplet dialkylcarbene. A previous EPR study deduced that **2T** and triplet diphenylcarbene (DPC) have similar C–C–C bond angles at the carbene carbon.[4,9] The kinetic data demonstrate that **2T** and triplet DPC also react with methanol with comparable rate constants, implying that these two carbenes also have comparable singlet–triplet energy separations.

Acknowledgment. Support of this work by the National Science Foundation (CHE-8814950 Ohio State University, CHE-8800448 Princeton) is gratefully acknowledged.

(8) (a) Closs, G. L.; Rabinow, B. E. *J. Am. Chem. Soc.* **1976**, *98*, 8196. (b) Eisenthal, K. B.; Turro, N. J.; Sitzmann, E. V.; Gould, J. R.; Hefferon, G.; Langan, J.; Cha, Y. *Tetrahedron* **1985**, *41*, 1543. (c) Griller, D.; Nazran, A. S.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 198.

(9) Brandon, R. W.; Closs, G. L.; Davoust, C. E.; Hutchinson, C. A., Jr.; Kohler, B. E.; Silbey, R. *J. Chem. Phys.* **1965**, *43*, 2006.

Non-Electron-Transfer Quinone-Mediated Oxidative Cleavage of Cyclopropylamines. Implications Regarding Their Utility as Probes of Enzyme Mechanism[1]

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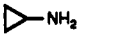
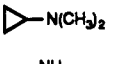
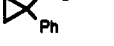
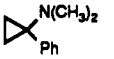
Summary: 3,5-Di-*tert*-butyl-1,2-benzoquinone effects oxidative cleavage of cyclopropylamine (CPA) and its 1-phenyl analogue via *o*-quinoneimine intermediates, a reaction which may serve as a model for the inactivation of plasma amine oxidase by CPA.

Mechanistic diversity in the biological oxidation of amines is an important problem of substantial current research focus. Oxidative ring opening of cyclopropylamines has been a useful mechanistic probe for enzymes thought to oxidize amines by initial one-electron oxidation at nitrogen.[2] Cyclopropylamine (CPA) is also an inactivator[3] of plasma amine oxidase (PAO) a copper-containing enzyme which utilizes a covalently bound quinone cofactor for effecting a pyridoxal-like transamination of primary amines to aldehydes.[4] This cofactor was believed to be pyrroloquinoline quinone (PQQ),[5] but has recently been demonstrated to be the oxidized form of a protein-based 2,4,5-trihydroxyphenylalanine residue.[6] Herein we report on a quinone-mediated oxidative cleavage of cyclopropylamines which is not initiated via one-electron oxidation at nitrogen, and which may serve as a model reaction for investigating the mechanism of copper amine oxidases.

Table I

amine substrate	DTBQ[a] $t_{1/2}$ (h)	$Fe(CN)_6^{3-}$ $t^{1/2}$ (min)[b]
	0.3 (first stage) 38. (second stage)	94.2
	23.	9.0
	12.5	356.
	35.	17.3

[a] $[amine]_0$ = $[DTBQ]_0$ = 1.25 mM, 31 °C, pH = 9.0 (2.5 mM carbonate), 50% aqueous CH_3CN; following disappearance of quinone (or quinoneimine) band. [b] Pseudo-first-order conditions; $[amine]_0$ = 25.0 mM, $[Fe(III)]_0$ = 2.5 mM, [KOH] = 0.5 M, 25 °C; following disappearance of Fe(III).

In exploring preparative methods for the oxidative deamination of amines, Corey and Achiwa[7] found that the Michael-blocked quinone 3,5-di-*tert*-butyl-1,2-benzoquinone (DTBQ) efficiently converted *sec*-alkyl primary amines to ketones.[8] The transamination pathway proposed (Scheme I), involving aromatization to an aminophenol Schiff base, has now been firmly documented for several *o*-quinones.[9-11]

(1) Presented in preliminary form at the 197th National Meeting of the American Chemical Society, Dallas, April 9–14, 1989, Abstr ORGN 282.

(2) With cytochrome P-450: Macdonald, T. L.; Zirvi, K.; Burka, L. T.; Peyman, P.; Guengerich, F. P. *J. Am. Chem. Soc.* **1982**, *104*, 2050. Hanzlik, R. P.; Tullman, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 2048. With monoamine oxidase: Silverman, R. B. *J. Biol. Chem.* **1983**, *258*, 14766. Silverman, R. B.; Zieske, P. A. *Biochemistry* **1985**, *24*, 2128.

(3) Abeles, R. H. In *Enzyme Activated Irreversible Inhibitors*; Seiler, N., Jung, M. J., Koch-Weser, J., Eds.; Elsevier: Amsterdam, 1978; p 9. We have confirmed that 3 mM CPA results in a 80–85% loss of bovine plasma amine oxidase (Sigma) activity in 30 min at 30 °C.

(4) (a) Farnum, M.; Palcic, M.; Klinman, J. P. *Biochemistry* **1986**, *25*, 1898. (b) Knowles, P. F.; Pandeya, K. B.; Rius, F. X.; Spencer, C. M.; Moog, R. S.; McGuirl, M. A.; Dooley, D. M. *Biochem. J.* **1987**, *241*, 603.

(5) Duine, J. A.; Frank, J.; Jongejan, J. A. *Adv. Enzymol.* **1987**, *59*, 169.

(6) Janes, S. M.; Mu, D.; Wemmer, D.; Smith, A. J.; Kaur, S.; Maltby, D.; Burlingame, A. L.; Klinman, J. P. *Science* **1990**, *248*, 981. Certain other copper amine oxidases appear to contain different protein-based quinone cofactors.

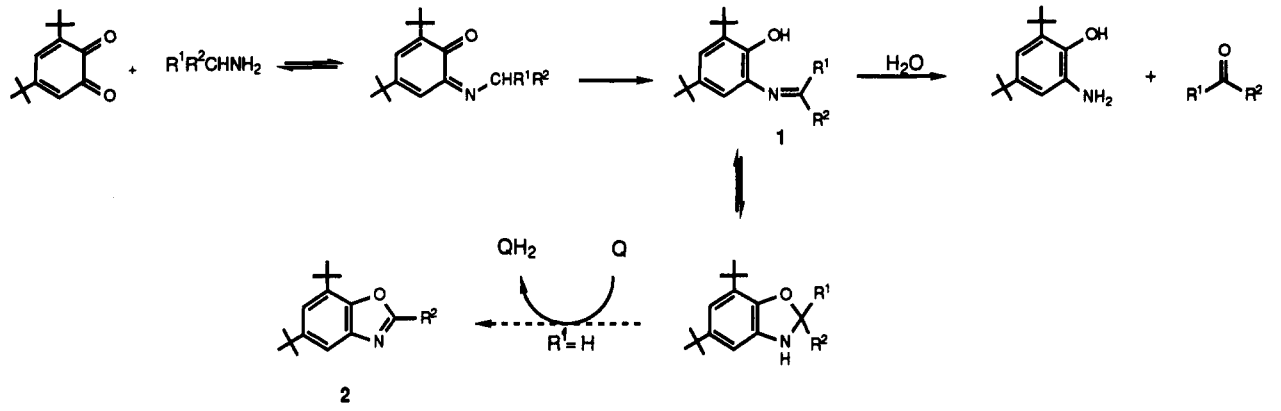
(7) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429.

(8) DTBQ is not useful for converting unbranched primary amines to aldehydes because the initial product **1** is in equilibrium with an oxidizable dihydrobenzoxazole (R^1 = H), giving benzoxazole **2**. We found this oxidation to be mediated by the quinone and not by O_2, as determined by independent synthesis of **1** from 2-amino-4,5-di-*tert*-butylphenol and aldehyde. Such DTBQ-mediated oxidation has been pointed out previously: Vander Zwan, M. C.; Hartner, F. W.; Reamer, R. A.; Tull, R. *J. Org. Chem.* **1978**, *43*, 509.

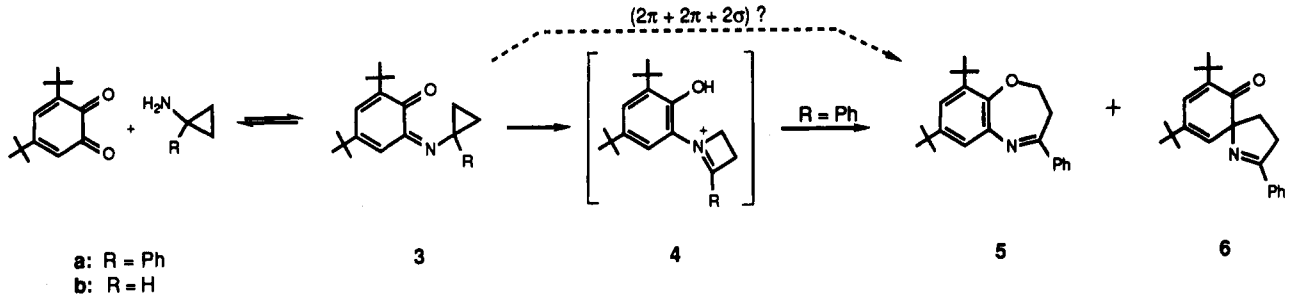
(9) (a) Eckert, T. S.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 4431. (b) Sleath, P. R.; Noar, J. B.; Eberlein, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1985**, *107*, 3328. (c) Rodriguez, E. J.; Bruice, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 7947.

0022-3263/91/1956-1353$02.50/0

Scheme I



Scheme II



a: R = Ph
b: R = H

DTBQ reacts with 1-phenylcyclopropylamine (1-PCPA) in pH 9 carbonate-buffered 1:1 CH_2CN–H_2O to produce a mixture of dihydrobenzoxazepine **5a** and the azaspirodecatrienone **6a** (Scheme II).[12] The intermediacy of **3a** is discernible at high concentration (12.5 mM, 10–15 °C) in the form of a rapid initial 15% absorbance *increase* (λ_{max} shifts from 407 to 395 nm)[13] prior to the onset of the chromophore bleaching normally observed in quinone–amine reactions. Interestingly, product **5a** began to crystallize in the spectrophotometric cuvet just after peaking of the 395-nm absorbance assigned to **3a**. A concerted mechanism operating for the synisomer of **3a** can rationalize formation of **5a** from **3a**, but a nitrenium-like ring expansion of **3a** to dehydroazetidinium species **4a** (Scheme II) can explain both products and finds precedent in the oxidative cleavage of cyclopropylamines by $Pb(OAc)_4$[14] and by HOCl.[15] Other mechanisms are also possible.

The intermediacy of *o*-quinoneimine is seen more clearly for the reaction between DTBQ and CPA (1.25 mM, 31 °C). In this case, the *o*-quinone band at 407 nm is replaced by a 2 times more intense absorbance at 392 nm,[13] which then slowly decays in isosbestic fashion (Table I). Our assignment of the initial spectral change in terms of **3b** is supported by the observation of parallel changes in the ^1H NMR spectrum, namely shifts of both the CPA C_α-H multiplet (from δ 2.19 to 3.67) and the downfield quinone vinyl doublets. The *final* products obtained from CPA are complex,[16] but NMR clearly indicates conversion of the *o*-quinoneimine initially to a single ring-opened intermediate (4 H multiplet at δ 3.09 and 1 H aryl doublets at δ 7.32 and 7.54).[17] Intermediate *o*-quinoneimines are not normally observed in reactions between DTBQ and simple primary amines due to rapid tautomerization,[11] but the latter is disfavored in the case of CPA on account of geometrical strain: the CPA- and 1-PCPA-derived *o*-quinoneimines are thus stable until the ring-opening process sets in.[18] In fact, the reaction of CPA with the more weakly oxidizing *p*-quinone 2,6-di-*tert*-butyl-1,4-benzoquinone under the same conditions gives an isolable *p*-quinoneimine,[12] which gives cleavage products only upon extensive heating.

We further compared the rates of DTBQ oxidation of CPA and 1-PCPA to those for the corresponding *N*,*N*-dimethyl tertiary amines (Table I). Although only primary amines can form quinoneimine intermediates, secondary and tertiary amines react with quinones through alternative covalent intermediate mechanisms.[9a,b] It is clear from Table I that the primary amines are more reactive with DTBQ than are the tertiary amines, as expected for a reaction proceeding through Schiff base intermediates. In

(10) Itoh, S.; Kitamura, Y.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1907.
(11) Klein, R. F. X.; Bargas, L. M.; Horak, V. *J. Org. Chem.* **1988**, *53*, 5994.
(12) Compounds were characterized by 200-MHz ^1H NMR, ^{13}C NMR, HRMS, and UV.
(13) Precedent for the observed spectral changes is the 10% increase in ϵ and shift of λ_{max} from 407 to 398 seen upon titrating DTBQ with NH_3 (as NH_4OH). Monoquinoneimine formation from PQQ was reported to be associated with a small ϵ increase: Mure, M.; Itoh, S.; Ohshiro, Y. *Tetrahedron Lett.* **1989**, *30*, 6875. The larger spectral perturbation observed for CPA might be due to *o*-quinoneimine conjugation with the cyclopropane ring.
(14) Hiyama, T.; Koide, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2918.
(15) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26.
(16) One final product isolated has a "dimeric" MW of 518, and ^1H NMR shows it to be an adduct between an unidentified CPA-ring-opened/DTBQ product and the initial quinoneimine **3b** (with cyclopropyl ring intact). Details of all DTBQ reactions will be described later in a full paper.
(17) This intermediate may correspond to the tricyclic aminoether tautomer of **4b**, where the phenolic OH has added to the iminium carbon, or to the simple H_2O adduct (a carbinolamine); it becomes long-lived if CPA is reacted with *excess* (e.g., 3 equiv) DTBQ in CD_3CN–D_2O containing a trace of NaOD.
(18) *trans*-2-Phenylcyclopropylamine (tranylcypromine) reacts very rapidly with DTBQ, and even at 12.5 mM dilution, the kinetics follow clean isosbestic behavior, so that any *o*-quinoneimine intermediate formed here must be very short-lived. A radical reaction cannot be ruled out in this case.

contrast to the DTBQ reactions, oxidation of our same series of amines by an authentic one-electron oxidant, alkaline ferricyanide (Table I), exhibits the expected tertiary > primary rate trend for a rate-limiting one-electron oxidation at nitrogen.[19] Since the reactions of CPA/1-PCPA with DTBQ involve spectroscopically observable intermediates with cyclopropane ring intact, and follow a reactivity rank order opposite to that seen with Fe(III), it seems clear that the *initial* bimolecular encounters between these amines and DTBQ are not single electron transfer reactions.[20] The mechanisms of cyclopropane cleavage which occur subsequent to *o*-quinoneimine formation are not resolved at this time and may be heterolytic or may involve radical intermediates.[21]

These results should be viewed alongside other reports of enzymatic cyclopropane cleavages which appear to proceed through non-electron-transfer mechanisms.[22] Thus, although initial one-electron oxidation of cyclopropylamines clearly results in ring opening,[23] other mechanistic pathways can also lead to cleavage products,[24] an important point in regard to the increasingly popular utilization of cyclopropanes in the design of novel enzyme inhibitors.[25]

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Supplementary Material Available: Spectral data on new compounds described (1 page). Ordering information is given on any current masthead page.

(19) Lindsay Smith, J. R.; Mead, L. A. V. *J. Chem. Soc., Perkin Trans. 2* **1973**, 206. Audeh, C. A.; Lindsay Smith, J. R. *J. Chem. Soc. B* **1970**, 1280.

(20) 1e oxidation of *tertiary* amines has been reported for high-potential quinones such as chloranil: Buckley, D.; Dunstan, S.; Henbest, H. B. *J. Chem. Soc.* **1957**, 4880.

(21) For example, a chain reaction involving one-electron-reductive cleavage of **3a** can also rationalize formation of **6a**, and both **5a**/**6a** could form via collapse of a semiquinoid-homoallylcarbinyl diradical generated via homolysis of **3a**.

(22) Suckling, C. J. *Biochem. Soc. Trans.* **1986**, *14*, 402.

(23) Qin, X.-Z.; Williams, F. *J. Am. Chem. Soc.* **1987**, *109*, 595.

(24) Both 1e and 2e oxidants are known to cleave 1-aminocyclopropanecarboxylic acid: Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207. Baldwin, J. E.; Jackson, D. A.; Adlington, R. M.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 206. Vaidyanathan, G.; Wilson, J. W. *J. Org. Chem.* **1989**, *54*, 1815.

(25) Suckling, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 537.

Self-Reproduction of Chirality. Asymmetric Synthesis of β-Aryl-β-amino Acids from Enantiomerically Pure Dihydropyrimidinones

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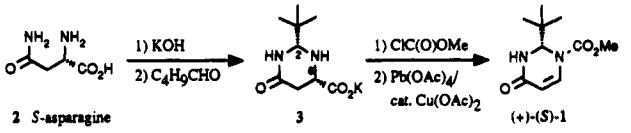
Summary: Enantiomerically pure dihydropyrimidinone **1** reacts with aryl iodides in the presence of catalytic amounts of $Pd(OAc)_2$ and added phosphine to afford dihydropyrimidinone **4**, in which a formal conjugate addition of the aryl group to the α,β-unsaturated system has occurred. Application of this methodology to the synthesis of a protected version of the tripeptide portion of the natural product jasplakinolide is presented.

Chemical methods for the production of enantiomerically pure α-amino acids have been the focus of much research activity in recent years.[1] Conversely, there are relatively few methods for the synthesis of chiral, nonracemic β-amino acids,[2] although there is considerable interest in these compounds as precursors to β-lactams,[3,4] as components of natural products[5] and as reactive molecules in their own right.[6] As part of our synthetic effort toward (+)-jasplakinolide,[7–9] which contains the β-amino acid (*R*)-β-tyrosine,[10] we became intrigued with the prospect of a synthetic method in which introduction of the desired *carbon substituent* at the β-site could be achieved in an enantioselective manner. This approach contrasts with previous methodologies, which develop the chiral center via conjugate addition of an amine to an α,β-unsaturated system,[11] reduction of a C=C or C=N functionality,[12] or C—C bond formation involving imines and carbon nucleophiles.[13] Herein we report our initial results on the use of novel heterocycle **1** as a *reagent* for the synthesis of enantiomerically pure aromatic β-amino acids.

Scheme I



The synthesis of (+)-(*S*)-**1** (Scheme I) proceeds via pivaldehyde acetalization of the potassium salt of (*S*)-

† American Cancer Society Junior Faculty Research Awardee, 1987–90.

(1) For recent developments in the area of α-amino acid synthesis, see: (a) O'Donnell, M. J. *Tetrahedron* **1988**, *44*, 5253–5614. (b) Williams, R. M. *The Synthesis of Optically Active α-Amino Acids*; In Organic Chemistry Series; Baldwin, J. E., series Ed.; Pergammon Press: Oxford, 1989.

(2) (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: New York, 1985; pp 25–54. (b) Griffith, O. W. *Ann. Rev. Biochem.* **1986**, *55*, 855–78.

(3) (a) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.* **1981**, *103*, 2406–8. (b) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056–9. (c) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328–43. (d) Davies, S. G.; Dordor-Hedgecock, I. M.; Sutton, K. H.; Walker, J. C. *Tetrahedron Lett.* **1986**, *27*, 3787–90. (e) Kim, S.; Chang, S. B.; Lee, P. H. *Tetrahedron Lett.* **1987**, *28*, 2735–6.

(4) β-Lactams are also useful synthons. See: (a) Ojima, I.; Chen, H.-J. C.; Nakahashi, K. *J. Am. Chem. Soc.* **1988**, *110*, 278–81. (b) Wasserman, H. H. *Aldrichim. Acta* **1987**, *20*, 63–74.

(5) Some examples of the natural products containing β-amino acids are as follows: (a) Blasticidin S: Yonehara, H.; Otake, N. *Tetrahedron Lett.* **1966**, 3785. (b) Bleomycin: Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383–91. (c) Bottromycin: Waisvisz, J. M.; van der Hoeven, M. G.; Nijenhuis, B. *J. Am. Chem. Soc.* **1957**, *79*, 4524. Nakamura, T.; Chikaike, H.; Yonehara, H.; Umezawa, H. *Chem. Pharm. Bull.* **1965**, *13*, 599. (d) Edeine: Hettinger, T. P.; Craig, L. C. *Biochemistry* **1966**, *7*, 4147–53. (e) Scytonemin A: Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298–1307.

(6) For example, see: Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519–21.

0022-3263/91/1956-1355$02.50/0