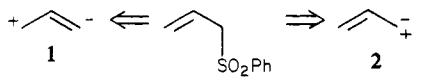
Allyl Sulfones as Synthons for 1,1- and 1,3-Dipoles via Organopalladium Chemistry

Sir:

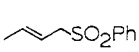
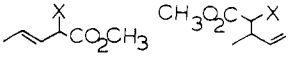
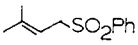
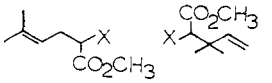
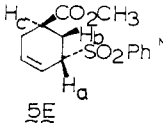
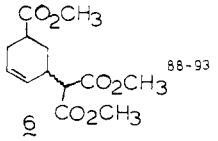
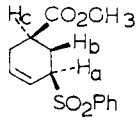
The sulfone group has proven exceedingly useful via its ability to stabilize an adjacent carbanion, but it generally fails to serve as a leaving group in nucleophilic displacements.[1-3] If, by choosing the appropriate metal reagent, it could become possible to restructure the reactivity profile of the allyl sulfone from a nucleophile to an electrophile, the allyl sulfone would become the functional equivalent of either a 1,3-dipole (**1**) or a 1,1-dipole (**2**). In this



communication, we report the realization of this equivalency via the heretofore unrecognized ability of the allyl sulfone to undergo oxidative addition to palladium(0), which results in a chemoselective alkylation.[4,5]

The simple allyl sulfones were generally prepared by reaction of the allyl halide with sodium benzenesulfinate.[6,7] Treatment of the allyl sulfone with approximately 5 mol % of a palladium(0) complex in the presence of a soft nucleophile at room temperature or reflux in THF led to a smooth alkylation as summarized in Table I. For disubstituted olefins (entries 1, 2, 3, 5, and 6), tetrakis(triphenylphosphine)palladium (**7**) served as catalyst, but the sterically less demanding bis[bis(1,2-diphenylphosphinoethane)]palladium (**8**) was required for the trisubstituted olefin (entry 4). Initial attempts to determine the stereochemistry of the alkylation (entries 5 and 6) were thwarted by the rapid epimerization of the starting allyl sulfone [(*E*)-**5**[7,8] (57 ± 1%) ⇌ (*Z*)-**5**[7,8] (43 ± 1%)]. Thus, (*E*)-**5** gave a 59:41 mixture of (*E*)-**6**[7,8] and (*Z*)-**6**,[7,8] and (*Z*)-**5** gave a 58:42 mixture. This product ratio is that expected if the products were formed from the equilibrium mixture of (*E*)-**5** and (*Z*)-**5** with net retention of configuration.

Table I. Allylic Alkylation of Simple Allyl Sulfones

Entry	Allyl Sulfone	Nucleophile	Product		Yield
1[a]	**3** R=CH3	$NaCH(CO_2CH_3)_2$	**4** R=CH3		74
2[a]	**3** R=Ph	$NaCH(CO_2CH_3)_2$	**4** R=Ph		71
3					
	$a^{a,i}$	$NaCH(CO_2CH_3)_2$	X=CO_2CH_3	73	27	71
	$b^{c,i}$	$NaPhSO_2CHCO_2CH_3$	X=$PhSO_2$	66	34	73
4					
	$a^{b,j}$	$NaCH(CO_2CH_3)_2$	X=CO_2CH_3	60	40	75
	$b^{b,j}$	$NaPhSO_2CHCO_2CH_3$	X=$PhSO_2$	78	22	68
5		$NaCH(CO_2CH_3)_2$			88-93
	5E		**6**		
6		$NaCH(CO_2CH_3)_2$	**6**		71

[a] Catalyst employed was tetrakis(triphenylphosphine)palladium (**7**). [b] Catalyst employed was bis[bis(1,2-diphenylphosphinoethane)]palladium (**8**). [c] Catalyst prepared *in situ* from palladium chloride and DIBAL-H in the presence of 1,2-diphenylphosphinoethane. [d] Reference 7. [e] Ratio of products determined by ratio of vinyl protons of disubstituted olefin at δ 5.21–5.65 and of monosubstituted olefin at δ 4.98 (ddd, J = 10.3, 1.6, 0.8 Hz), 5.06 (ddd, J = 17.3, 1.5, 1.2 Hz), and 5.75 (ddd, J = 17.3, 10.3, 7.9 Hz). [f] Ratio of products determined by ratio of vinyl methyl absorption at δ 1.61 (dd, J = 6.5, 1.0 Hz) to saturated methyl absorption at δ 1.12 and 1.36 (each, d, J = 6.9 Hz, diastereomeric mixture). [g] Ratio of products determined by ratio of vinylmethyl absorptions at δ 1.65 and 1.70 to saturated methyl absorption at δ 1.25. [h] Ratio of products determined by ratio of absorptions of methine proton α to the sulfone at δ 3.93 (t, J = 7.4 Hz) and δ 3.48 (s). [i] Reference 6. [j] Reference 9. [k] Reference 8. (*E*)-**5**, mp 70.5–71 °C. (*Z*)-**5**, mp 90 °C.

Use of the allyl sulfones as nucleophiles[1] led to clean α substitution (eq 1–4). Now, inverting the reactivity of the allyl sulfone by using a palladium(0) catalyst in the presence of a nucleophile led to attack predominantly (normally >90%) at the less substituted end of the allyl unit (eq 1, 3, and 4). This combination represents the equivalence of a 1,3-dipole as pictured. In the case of **9a**, the dependency of the regioselectivity on the choice of catalyst was examined; there was only a minor dependency (primary vs. secondary, 91:9 with $[(CH_3O)_3P]_4Pd$ to 95:5 with **8**). The steric demands of the nucleophile are more pronounced.[16,17] For **9b**, use of the anion of dimethyl malonate led to **10b** (X = CO_2CH_3) and the product from attack at the secondary carbon in a 83:17 ratio; use of the anion of methyl benzenesulfonylacetate led to the corresponding products in a 93:7

(1) For most recent examples, see: Janssen, C. G. M.; van Lier, P. M.; Buck, H. M.; Godefroi, E. F. *J. Org. Chem.* **1979**, *44*, 4199; Hauser, F.; Rhee, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 1628: Trost, B. M.; Verhoeven, T. R. *Ibid.* **1979**, *101*, 1595. Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2429. Durst, T.; Tin, K.-C.; de Reinach-Hirtzbach, F.; Decesare, J. M.; Ryan, M. D. *Can. J. Chem.* **1979**, *57*, 258. Inomata, K.; Nakayama, U.; Tsutsumi, M.; Kotaki, H. *Heterocycles* **1979**, *12*, 1467. Reutrakul, V.; Tuchinda, P.; Kusamran, K. *Chem. Lett.* **1979**, 1055. Trost, B. M.; Verhoeven, T. R. Fortunak, J. *Ibid.* **1979**, 2301. Kocienski, P. J.; Tideswell, J. *Synth. Commun.* **1979**, *9*, 411. Little, R. D.; Wolf, S.; Smestad, T.; Seike, S. C.; Linler, C. W., Jr.; Patton, L. *Ibid.* **1979**, *9*, 545. Ueno, Y.; Setoi, H.; Okawara, M. *Chem. Lett.* **1979**, 47; Orr, D. *Synthesis* **1979**, 139. Hauser, F.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. Chang, Y. H.; Pinnick, A. W. *Ibid.* **1978**, *43*, 373. Bartlett, P. A.; Green, F. R., III; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829. Torii, S.; Uneyama, K.; Kawahara, I. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 949. Corbel, B.; Decesare, J. M.; Durst, T. *Can. J. Chem.* **1978**, *56*, 505. Saddler, J. C.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.*, **1978**, 5079; Wildeman, J.; Borgen, P. C.; Pluim, H.; Rouwette, P. H. F. M.; van Leusen, A. M. *Ibid.* **1978**, 2213. Trost, B. M.; Verhoeven, T. R. *Ibid.* **1978**, 2275. Metcalf, B. W.; Bonilavri, E. *J. Chem. Soc., Chem. Commun.* **1978**, 914. Shono, T.; Matsumura, Y.; Kashimura, S. *Chem. Lett.* **1978**, 69. Takayanagi, H.; Uyehara, T.; Kato, T. *Ibid.* **1978**, 359. Stetter, H.; Bender, H. J. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 131. For an excellent review of earlier work, see: Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.

(2) Kraus, G. A.; Frazier, K. *Synth. Commun.* **1978**, *8*, 483.

(3) (a) For organocopper chemistry and sulfones, see: Julia, M.; Righini, A.; Verpeaux, J. N. *Tetrahedron Lett.* **1979**, 2393. (b) Sulfones have served as a leaving group for cyclopropane formation: Parker, W. L.; Woodward, R. B. *J. Org. Chem.* **1969**, *34*, 3085. Campbell, R. V. M.; Crombie, L.; Findley, D. A. R.; King, R. W.; Pattenden, G.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 897. Also see ref 9.

(4) For a synthesis of allyl sulfones via a palladium-catalyzed addition to dienes, see: Julia, M.; Nel, M.; Saussine, L. *J. Organomet. Chem.* **1979**, *181*, C17.

(5) For a nickel- and palladium-catalyzed arylation of allyl sulfides, see: Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425.

(6) For a review, see: Durst, T. *Compr. Org. Chem.* **1979**, *3*, 171 ff, 197ff.

(7) New compounds have been characterized by spectral means and elemental composition (high-resolution mass spectrometry and/or elemental analysis).

(8) Assignment of stereochemistry stems from the equilibration studies and NMR data. (*E*)-**5** (270 MHz): δ 3.82 (H_a, $W_{1/2}$ = 12 Hz, eq), 1.69 (H_b), 2.94 (H_c, $W_{1/2}$ = 25 Hz, ax; J_{ab} = 6.6 Hz, J_{bc} = 10.6 Hz). (*Z*)-**5** (270 MHz): δ 3.85 (H_a, $W_{1/2}$ = 24 Hz, ax), 2.00 (H_b), 2.46 (H_c, $W_{1/2}$ = 31 Hz, ax, J_{ab} = 11.5 Hz, J_{bc} = 13.0 Hz). (*E*)-**6** (270 MHz): δ 3.03 (H_a, $W_{1/2}$ = 17 Hz, eq ⇌ ax). (*Z*)-**6** (270 MHz): δ 2.98 (H_a, $W_{1/2}$ = 22 Hz, ax).

(9) Julia, M; Guy-Rouault, A. *Bull. Soc. Chim. Fr.* **1967**, 1411. Martel, J.; Huynh, C. *Ibid.* **1967**, 985.

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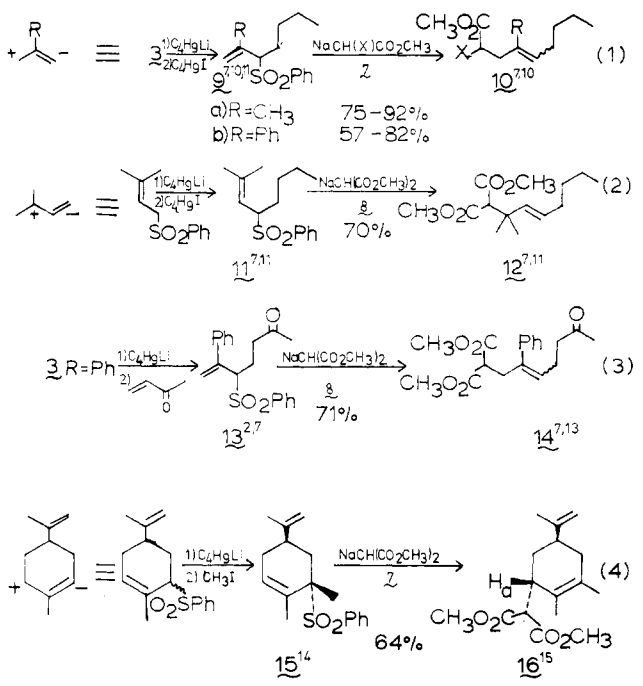
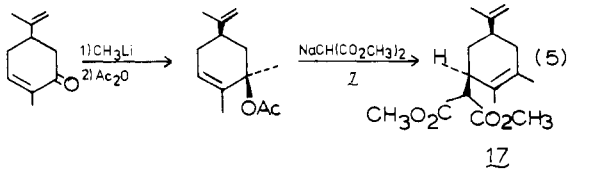
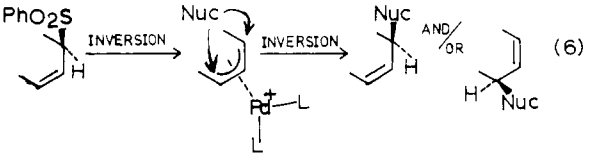


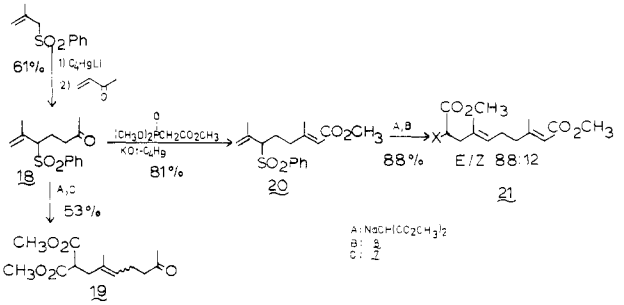
ratio.[10] It is interesting to note that the presence of the polar carbonyl function in the aliphatic chain as in **13** (eq 3) led exclusively to the product of attack at the primary carbon, i.e., **14**.[13] The only exception to this preference for attack at the less substituted carbon was the case of sulfone **11** (eq 2). An unprecedented preference for attack at the tertiary carbon to give **12** vs. attack at the secondary carbon (~90:10) was observed.[12] The question of stereochemistry was determined with **15**,[7,14] which led to the product **16**[3,15] of net retention but with allyl inversion, with approximately 5% crossover. The alternative isomer **17** was available as shown in eq 5. Thus, as depicted in eq 6, both the



oxidative addition and the nucleophilic attack occur with inversion of configuration.[16-18]

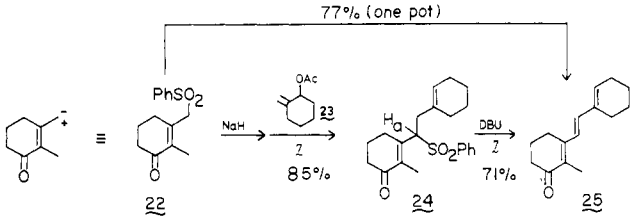


The chemoselectivity of this approach for C–C bond formation is highlighted by the short synthesis of the sex pheromone of the Monarch butterfly.[16b,19] The keto sulfone **18** was a substrate for



the palladium reaction, without the need to protect the carbonyl group, to give **19**[7,20] with complete regioselectivity. On the other hand, use of a typical carbonyl reagent, a phosphonate anion, led to the olefination product **20** without complications from the allyl sulfone. Addition of the palladium catalyst **8** and the anion of dimethyl malonate led in a regioselective alkylation to **21** (X = CO_2CH_3), which has previously been decarbomethoxylated to the dimethyl ester of the butterfly pheromone **21**[16b,19b,c] (X = H).

In a variant of this concept, use of the allyl sulfone as a nucleophile in a palladium-catalyzed alkylation and then as an electrophile in a palladium-catalyzed elimination[20] led to a new alkylative elimination, the result being the use of the allyl sulfone as a 1,1-dipole.[21] Conversion of **22** to its anion with sodium



hydride and reaction with allyl acetate **23** in the presence of about 5 mol % of **7** in THF containing 4 vol % of HMPA at reflux gave the product **24** [δ 4.41 (H_a, dd, J = 11.1, 4.1 Hz)] of exclusive γ alkylation (with respect to the carbonyl group of **22**). *Attempts to effect a simple base-catalyzed elimination of* **24** *failed.*[28] However, palladium-initiated ionization of the sulfone allowed smooth elimination at 80 °C in Me_2SO to the trienone **25**,[7,22] a model for pre-vitamin D. This duality of reactivity of the sulfone allowed a one-pot reaction in which the anion of **22** in Me_2SO was reacted with allyl acetate **23** in the presence of 3.6 mol % of **7** at room temperature and then 50 °C. Addition of 1.1 equiv of DBU and raising the temperature to 80 °C led to **25** in 77%

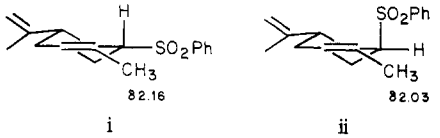
(10) **9a**, mp 50–53 °C. (*E*)-**10a** (X = CO_2CH_3): δ 5.26 (td, J = 7.6, Hz). (*Z*)-**10a**: 5.31 (m); *E*/*Z* 90:10, with very minor absorptions at δ 4.82 and 4.87 (each, brs) assigned to terminal methylene group. (*E*)-**10b** (X = CO_2CH_3): δ 5.69 (t, J = 7.4 Hz). (*Z*)-**10b**: δ 5.53 (t, J = 7.4 Hz); *E*/*Z* 78:22, with very minor absorptions at δ 5.07 and 5.31 (each, brs) for terminal methylene group. (*E*)-**10b** (X = $PhSO_2$): δ 5.70 (t, J = 7.4 Hz). (*Z*)-**10b**: δ 5.51 (t, J = 7.41 Hz); *E*/*Z* 77:23, with very minor absorptions at δ 5.01, 5.06, 5.32, 5.36 (each, brs, two diastereomers).

(11) Analogous to the procedure of Kocienski, P. J. *Tetrahedron Lett.* **1979**, 441.

(12) **12**: δ 5.58 (dt, J = 15.6, 1.1 Hz), 5.40 (dt, J = 15.6, 6.6 Hz), with minor absorptions at 1.63 and 1.68 (each, d, J = 1.3 Hz) for minor regioisomer.

(13) (*E*)-**14**: δ 5.63 (t, J = 6.9 Hz). (*Z*)-**14**: δ 5.52 (t, J = 7.1 Hz).

(14) **15**, mp 78.5–79 °C. The stereochemistry can be assigned on the basis of the deshielding of the vinylmethyl group by a pseudoequatorial benzenesulfonyl group, i.e., δ 2.03 in **15** where this group is pseudoaxial and δ 2.21 in the epimer at C(3) where it is pseudoequatorial; cf. i and ii.



i ii

(15) **16**: δ 2.97 (H_a, $W_{1/2}$ = 17 Hz, eq ≈ ax). **17**: δ 2.95 (H_a, $W_{1/2}$ = 20 Hz, ax).

(16) (a) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* **1976**, *41*, 3215. (b) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426.

(17) For a review, see: Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.

(18) Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611. Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *Ibid.* **1978**, *100*, 3416. Trost, B. M.; Verhoeven, T. R. *Ibid.* **1978**, *100*, 3435.

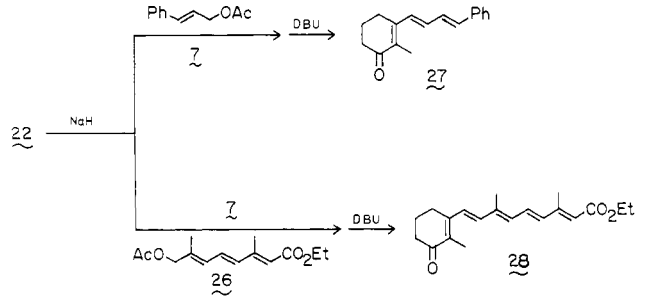
(19) (a) Miles, D. H.; Loew, P.; Johnson, W. S.; Kluge, A. F.; Meinwald, J. *Tetrahedron Lett.* **1972**, 3019; (b) Trost, B. M.; Weber, L. *J. Org. Chem.* **1975**, *40*, 3617. (c) Trost, B. M.; Frazee, W. J.; Salzmann, T. N.; Bogdenowicz, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 5512.

(20) For palladium-catalyzed eliminations, see: Trost, B. M.; Verhoeven, T. R.; Fortunak, J. *Tetrahedron Lett.* **1979**, 2301. Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Ibid.* **1978**, 2075. Hutchins, R. O.; Learn, K.; Fulton, R. P. *Ibid.* **1980**, 27.

(21) Cf.: (a) Julia, M.; Arnould, D. *Bull. Soc. Chim. Fr.* **1973**, 743, 746. (b) Kondo, K.; Tunemoto, D. *Tetrahedron Lett.* **1975**, 1007, 1397; Kondo, K.; Saito, E.; Tunemoto, D. *Ibid.* **1975**, 2275. (c) Julia, M.; Badet, P. *Bull. Soc. Chim. Fr.* **1975**, 1363. (d) Copper, G. K.; Dolby, L. J. *Tetrahedron Lett.* **1976**, 4675.

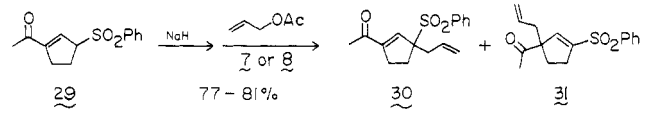
(22) **25**: mp 40–46 °C; IR 1646, 1598 cm^{-1}; 270-MHz NMR δ 1.91 (3 H, t, J = 1 Hz), 6.01 (1 H, brt, J = 4 Hz), 6.61 (s, 2 H); ^{13}C NMR (15.1 MHz) 122.5 (t), 130.8 (s), 134.3 (d), 136.0 (s), 138.1 (t), 149.9 (s).

yield (from **22**). Similarly, palladium-assisted alkylative elimination with cinnamyl acetate and the triene acetate **26** gave the



desired products **27**[7,23] and **28**[7,24] in 71% and 49% (~65% by high-pressure liquid chromatography analysis) yields after crystallization. The latter represents a model approach for possible Vitamin A metabolites and canthaxanthin.[25,26]

In an ancillary study, we noted that the choice of ligands on palladium had a pronounced effect on the α to γ ratio in the alkylation of γ-sulfonyl-α,β-unsaturated ketones.[27] For example, reaction of the sulfone **29** with allyl acetate and **7** gave a 3:2 ratio



of **30** and **31**; however, use of **8** as catalyst improved this ratio to 4:1. This flexibility of manipulating the reaction template and thereby manipulating the γ to α ratio is a decided advantage of transition-metal-catalyzed alkylations.

The dual reactivity accorded allyl sulfones substantially increases the role they can play in organic synthesis. Furthermore, this reversal of reactivity afforded by the transition metal highlights the application of such catalysts to generate new rules of selectivity.

Acknowledgments. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their continuing support of our programs. We also are grateful for a generous gift of ethyl 3,7-dimethyl-8-oxoocta-2,4,6-trienoate from Dr. Michael Rosenberger of the Hoffmann-La Roche Laboratories.

(23) **27**: mp 110 °C; IR 1648, 1600, 1589 cm^{-1}; 270-MHz NMR δ 1.95 (3 H, s), 6.70-7.00 (4 H, m), 7.25-7.43 (5 H, m); ^{13}C NMR (15.1 MHz) 126.5, 128.0, 128.4, 128.8, 130.5, 131.8, 134.8, 135.8, 136.5, 149.1.

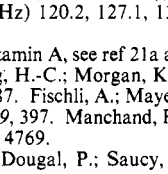
(24) **28**: mp 132-133.5 °C; IR 1700, 1648, 1598 cm^{-1}; 270-MHz NMR δ 1.96 (3 H, s), 2.05 (3 H, s) 2.36 (3 H, s), 5.78 (1 H, s), 6.34 (2 H, d, J = 13.4 Hz), 6.65 and 6.78 (2 H, AB, J = 15.4 Hz), 7.01 (1 H, dd, J = 13.4, 13.4 Hz); ^{13}C NMR (15.1 MHz) 120.2, 127.1, 130.1, 132.5, 134.5, 137.9, 138.6, 149.3, 151.8, 166.8.

(25) For allyl sulfones in Vitamin A, see ref 21a and earlier references cited therein: Olson, G. L.; Cheung, H.-C.; Morgan, K. D.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3287. Fischli, A.; Mayer, H.; Simon, W.; Stotler, H. J. *Helv. Chim. Acta* **1976**, *59*, 397. Manchand, P. S.; Wong, H. S.; Blount, J. F. *J. Org. Chem.* **1978**, *43*, 4769.

(26) Rosenberger, M.; McDougal, P.; Saucy, G.; Bahr, J. *Pure Appl. Chem.* **1979**, *51*, 871.

(27) Cf.: Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602.

(28) The failure of the simple base-catalyzed elimination in these cases compared to the many examples of such reactions apparently stems from the high acidity of H_a in iii, precluding the E_2 elimination.



iii

(29) NIH-NCI Postdoctoral Fellow, 1978-1980.

Barry M. Trost,* Norman R. Schmuff, Michael J. Miller[29]

McElvain Laboratories of Organic Chemistry
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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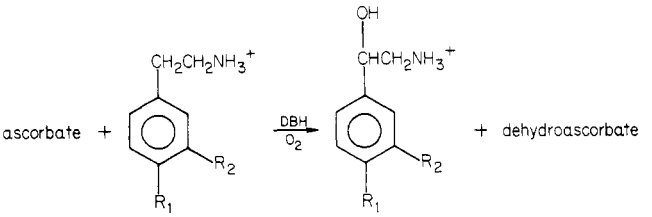
Asymmetric Sulfoxidation by Dopamine β-Hydroxylase, an Oxygenase Heretofore Considered Specific for Methylene Hydroxylation

Sir:

Dopamine β-hydroxylase (DBH) [EC 1.14.2.1], a copper-containing monooxygenase present in a variety of mammalian tissues,[1,2] catalyzes the conversion of dopamine to norepinephrine, thus playing a key role in the biosynthetic conversion of potent neurotransmitters and in the production of adrenaline.[3] Although a variety of 2-phenylethylamines substituted on either the aromatic ring or the alkyl chain have been examined as substrates, the only known oxygenase activity for this enzyme has been methylene hydroxylation at the benzylic position.[4] We now report that DBH stereoselectively catalyzes the conversion of phenyl 2-aminoethyl sulfides to the corresponding sulfoxides at a rate which is considerably higher than hydroxylation of the corresponding carbon analogues. To our knowledge, this is the first demonstration of sulfoxidation by an oxygenase which normally catalyzes only aliphatic hydroxylation.



Phenyl 2-aminoethyl sulfide (I), the prototype sulfide substrate, was synthesized by the method of Wehrmeister,[5] crystallized as the hydrochloride from EtOH/Et_2O, and characterized by NMR, plus mass spectral and elemental analysis [mp 162-163 °C (lit. 162-163 °C).[6] Anal. Calcd for $C_8H_{12}NSCl$: C, 50.65; H, 6.38; N, 7.38; S, 16.90. Found: C, 50.63; H, 6.38; N, 7.35; S, 16.89]. DBH was isolated and purified from bovine adrenals by using a modification of the method of Ljones et al.,[7] which is described elsewhere.[8] Incubation of I with highly purified DBH (sp act. 12-15 units/mg) in the presence of fumarate, copper,[9] and $Fe(CN)_6^{4-}$ or ascorbate as the electron donor results in an enzyme-dependent consumption of both electrons and O_2, in the

Table I. Stoichiometry of DBH-Catalyzed Oxygenation Reactions

oxygenated substrate	$[Fe(CN)_6^{4-}]$[a]/[substrate] consumed	$[O_2]$[b]/[substrate] $Fe(CN)_6^{4-}$	ascorbic acid	[product]/[substrate]
phenyl 2-aminoethyl sulfide (I)	2.1	0.8	0.9	1.2[c]
tyramine	2.1	1.0		*d*

[a] Determined by measuring A_{420} under substrate-limiting conditions. See footnote *a*, Table II, for details. [b] Measured with an O_2-sensitive polarographic electrode under substrate-limiting conditions. See footnote *b*, Table II, for details. [c] Determined from UV analysis of the product isolated by ion-exchange chromatography as described in the text, after O_2 and electron consumption had ceased. [d] The stoichiometry of product formed per 2 equiv of $Fe(CN)_6^{4-}$ has been reported as 1:1.[7]

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(8) Manuscript in preparation.

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