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Epoxides and Aziridines from Diazoacetates via Ylide Intermediates

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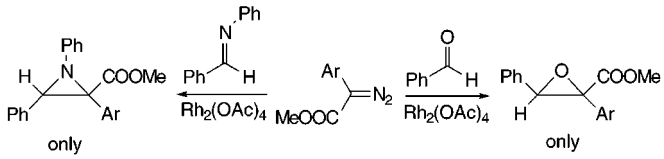
ABSTRACT

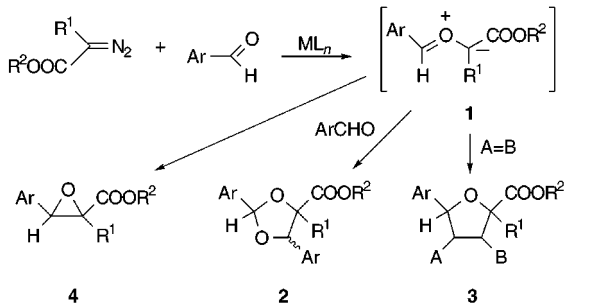


An effective methodology is reported for stereospecific epoxidation and aziridination via carbonyl ylide intermediates using rhodium(II) acetate catalyzed reactions of phenyl- and styryldiazoacetates with aldehydes, ketones, or imines.

In the long history of catalyst-directed entry to carbonyl ylides from diazocarbonyl compounds, there have been very few examples of epoxide formation.[1] Huisgen reported the formation of oxirane from the reaction of dimethyl diazomalonate with benzaldehyde, but in only 7% yield when the reaction was performed at 125 °C in the presence of 1 mol % of $Cu(acac)_2$;[2] the same compound was not reported in reactions performed with $Rh_2(OAc)_4$ or CuOTf at lower temperatures and might have been due to thermolysis. Maas reported epoxidation of benzaldehyde with α-diazo(trimethylsilyl)acetates, but only when CuOTf was used and only in competition with 1,3-dipolar addition;[3] the epoxidation product was not observed with catalysis by dirhodium(II) perfluorobutyrate. Instead, the initially formed carbonyl ylide **1** undergoes proton transfer, 1,3-dipolar cycloaddition, or internal reactions that are specific to the diazo compound employed (Scheme 1).[4] With ethyl diazoacetate (R^1 = H, R^2 = Et), for example, catalytic diazo decomposition in the presence of benzaldehyde resulted in dioxolane formation (**2**) and in **3** when performed in the presence of an alternative dipolarophile.[5] As a result of the apparent inability of diazo compounds to form epoxides directly via this methodology, Aggarwal has devised a clever alternative whereby an organic sulfide intercepts the metal carbene, and epoxidation of aldehydes takes place via a sulfur ylide.[6]

If one recognizes the absence of **4** from catalytic reactions of diazo compounds with aldehydes as a function of the relative rates for ring closure of **1** and reactions with dipolarophiles, then increasing the stability of the intermediate ylide might be expected to reverse the preference for dipolar cycloaddition. Indeed, some early photochemical results with diazo compounds did produce products from carbene addition to ketones,[7] but these results were not elaborated beyond means for detection of carbonyl ylide intermediates. We now report that catalytic diazo decomposi-

Scheme 1



(1) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley and Sons, Inc.: New York, 1998; Chapter 7. Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.

(2) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952.

(3) Alt, M.; Maas, G. *Tetrahedron* **1994**, *50*, 7435.

(4) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

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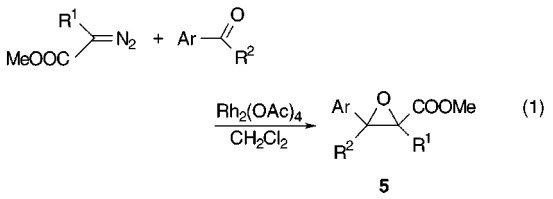
tion of phenyl- and styryldiazoacetates in the presence of arylaldehydes and aryl ketones results in stereospecific epoxidation and that when these reactions are performed with arylimines stereospecific addition occurs to produce a single aziridine product.



(1)

5

Addition of aryldiazoacetate or styryldiazoacetate to an equivalent amount of aldehyde in the presence of $Rh_2(OAc)_4$ resulted in the production of epoxide **5** (eq 1) as a single isomer in good yield. Product stereochemistry was established as Z by correlation of the product from epoxidation of the alkene corresponding to **5** (R^1 = Ph, R^2 = H, Ar = Ph) and from the X-ray structure of the product from reaction of methyl phenyldiazoacetate with *p*-anisaldehyde (Figure 1).[8,9] Complex mixtures were obtained with aliphatic aldehydes, but acetophenone gave **5** in modest yield, which could be increased by increasing the relative amount of ketone employed. Results are reported in Table 1. To determine relative reactivity, reaction between methyl phenyldiazoacetate and 5-fold molar excesses of benzaldehyde and styrene relative to methyl phenyldiazoacetate (eq 2) resulted in the formation of epoxide and cyclopropane products in a 2.1:1 ratio. Attempts to achieve enantiocontrol using chiral dirhodium azetidinone catalysts[10] were not successful; products obtained were racemic.

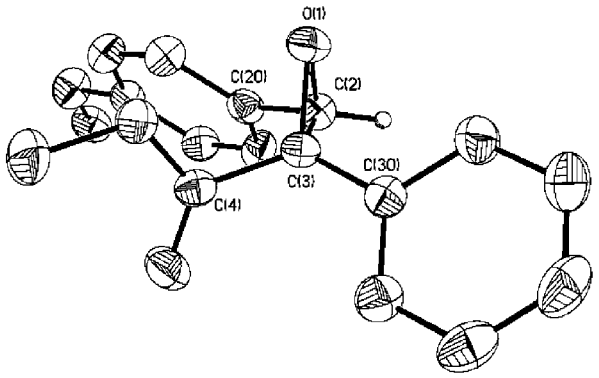
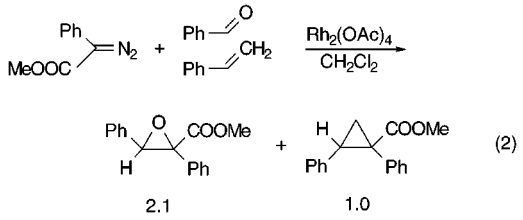


Figure 1. Crystal structure of 5 (R^1 = Ph, R^2 = H, Ar = *p*-$MeOC_6H_4$) with selected bond lengths [Å] and angles [deg]: O1−C2 1.442(3), O1−C3 1.435(3), C2−C3 1.482(3); C3−O1−C2 62.03(15), O1−C2−C3 58.76(15), O1−C3−C2 59.21(15); C20−C2−C3−C30 154.8(2).

Table 1. Isolated Yields of Epoxides **5** from Reactions of Diazoacetate with Aldehydes or Ketone[a]

R^1	Ar	R^2	yield **5**, %[b]
Ph	C_6H_5	H	66
Ph	*p*-$MeOC_6H_4$	H	81
Ph	*p*-$NO_2C_6H_4$	H	80
Ph	*t*-PhCH=CH[d]	H	86
Ph	C_6H_5	Me	38 (72)[c]
t-PhCH=H[d]	C_6H_5	H	50
t-PhCH=H[d]	*t*-PhCH=CH[d]	H	75

[a] Reactions performed in CH_2Cl_2 heated at reflux with 1.0 mol % of rhodium(II) acetate. [b] Isolated yield of product following chromatographic purification. [c] Yield obtained with 20-fold excess of acetophenone. [d] *t* = trans.



(2)

2.1 1.0

In a typical procedure, a solution of methyl phenyldiazoacetate (0.351 g, 2.0 mmol) in 5 mL of CH_2Cl_2 was added via syringe pump (5.0 mL/h) over 1 h to a solution of $Rh_2(OAc)_4$ (8.8 mg, 0.02 mmol) and *trans*-cinnamaldehyde (0.29 g, 2.2 mmol) in 10 mL of CH_2Cl_2 heated at reflux. After complete addition, the reaction mixture was cooled to room temperature and then passed through a short silica plug, which was subsequently washed with CH_2Cl_2 (20 mL). The solvent was removed, and a portion of the crude product was subjected to ^{1}H NMR analysis for determination of chemo- and diastereoselectivity. None of the cyclopropane or *trans*-epoxidation product was observed in the crude ^{1}H

(5) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. Doyle, M. P.; Forbes, D. C.; Xavier, K. R. *Russ. Chem. Bull.* **1998**, *47*, 932.

(6) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. Aggarwal, V. K. *Synlett* **1998**, 329.

(7) Scino, J. C.; McGimpsey, W. G.; Casal, H. L. *J. Am. Chem. Soc.* **1985**, *107*, 7204. Becker, R. S.; Bost, R. O.; Kolc, J.; Bertoniere, N. R.; Smith, R. L.; Griffin, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 1302.

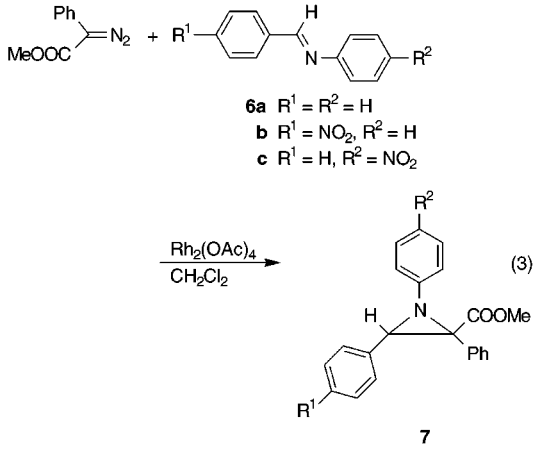
(8) Crystal data for **5** (R^1 = Ph, R^2 = H, Ar = *p*-$MeOC_6H_4$): $C_{17}H_{16}O_4$, M_r = 284.30, orthorhombic, space group *Pbca* with *a* = 11.8237(12), *b* = 8.4569(8), *c* = 28.946(3) Å, volume = 2894.4(5) Å^3, *Z* = 8, ρ_{calc} = 1.305 g/cm^3, *F*(000) = 1200. Colorless rectangular block (0.12 × 0.13 × 0.25 mm^3). Data were collected out to 2θ = 56° by an ω-scan technique (0.2° ωscan) and an exposure time of 20 s on a Bruker SMART 1000 CCD detector X-ray diffractometer at 170(2) K system using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). A total of 25430 reflections were integrated and retained, of which 3576 were unique (<redundancy> = 7.11, R_{int} = 9.4%, R_{sig} = 6.8%). Of the unique reflections, 1855 (52%) were observed $>2\sigma$(I). Solution was achieved utilizing direct methods followed by Fourier synthesis with anisotropic displacement parameters for the non-hydrogen atoms. Conventional refinement indices using the 1855 reflections with $F > 4\sigma(F)$ are R1 = 0.0601, wR2 = 0.1408. The structure was solved using SHELXS in the Bruker SHELXTL (version 5.0) software package.

(9) Crystallographic data (excluding structure factors) for **5** (R^1 = Ph, R^2 = H, Ar = *p*-$MeOC_6H_4$) and **7** (R^1 = R^2 = H) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-151857 and CCDC-151858. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, U.K. (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

(10) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.

NMR spectrum. Column chromatography on silica gel (hexanes/ethyl acetate = 20:1) yielded 0.48 g of *cis*-epoxidation product **5** as a viscous colorless oil in 86% yield.[11]

Addition to selected imines occurred in a similar fashion to furnish aziridine products in good yield. Methyl phenyldiazoacetate underwent $Rh_2(OAc)_4$-catalyzed reaction with arylimines **6** (eq 3) to produce a single isomer **7** (79% yield



with $R^1 = R^2 = H$, 64% yield with $R^1 = NO_2$, $R^2 = H$, and 84% yield with $R^1 = H$, $R^2 = NO_2$). In contrast to that of **5**, product stereochemistry for **7** was *E*, as determined by single-crystal X-ray diffraction studies (Figure 2).[12] With **7c** catalytic hydrogenation followed by ceric ammonium nitrate oxidation gave the NH-aziridine in good yield. There have been several recent reports of catalytic aziridination using ethyl diazoacetate but none using aryldiazoacetates, and in these cases the stereochemistry that predominates is opposite to that reported here.[13]

The results reported here are consistent with the intervention of ylide intermediates **8** and **9**. Steric interactions

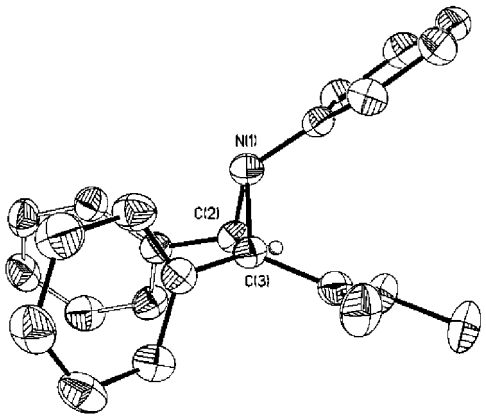
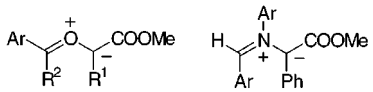


Figure 2. Crystal structure of 7 ($R^1 = R^2 = H$) with selected bond lengths (Å) and angles [deg]: N1−C2 1.450(2), N1−C3 1.469(2), C2−C3 1.524(2), N1−C3 1.469(2), C2−C20 1.488(2), C3−C30 1.498(2); C3−N1−C2 62.96(9), N1−C2−C3 59.13(9), N1−C3−C2 57.91.

between Ar and R^1 favor **8**. The *N*-aryl group controls stereochemical preference in **9** that results in the exclusive formation of **7**. In any case, only one diastereoisomer was observed for either epoxide or aziridine formation. These observations and interpretations suggest a broad versatility of this methodology for epoxidation and aziridination that has not been realized previously.



Acknowledgment. We are grateful to the National Science Foundation and to the National Institutes of Health (GM 46503) for their support of this research. We also acknowledge the Molecular Structure Laboratory at the University of Arizona, the NSF grant CHE9610374, which provided the diffractometer, and Dr. Michael Carducci for his assistance.

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(11) Methyl (2*R*/*S*,3*R*/*S*)-2,3-epoxy-2-phenyl-3-styrylpropionate (**5**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62−7.59 (comp, 2H), 7.45−7.29 (comp, 8H), 6.90 (d, J = 16.0 Hz, 1H), 6.08 (dd, J = 16.0, 7.9 Hz, 1H), 3.82 (s, 3H), 3.73 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 137.3, 135.7, 134.8, 128.7, 128.5, 128.4, 126.7, 126.6, 121.8, 65.7, 65.4, 52.7; HRMS calcd for $C_{18}H_{17}O_3$ 281.1178, found 281.1177.

(12) Crystal data for **7** ($R^1 = R^2 = H$): $C_{22}H_{19}NO_2$, M_r = 329.38, triclinic, space group *P*-1 with a = 8.2351(6), b = 10.7043(8), c = 11.2999(9) Å, α = 69.9100(10), β = 77.619(2), γ = 70.7020(10), volume = 877.19(12) Å^3, Z = 2, ρ_{calc} = 1.247 g/cm^3, $F(000)$ = 348. Colorless rectangular block (0.08 × 0.16 × 0.33 mm^3) cut from larger crystal. Data were collected and refined as described for **5**. Conventional refinement indices using the 2856 reflections with $F > 4\sigma(F)$ are R1 = 0.0484, wR2 = 0.1117.

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