ORGANIC LETTERS

2001
Vol. 3, No. 23
3741−3744

Highly Stereoselective Syntheses of Five- and Seven-Membered Ring Heterocycles from Ylides Generated by Catalytic Reactions of Styryldiazoacetates with Aldehydes and Imines

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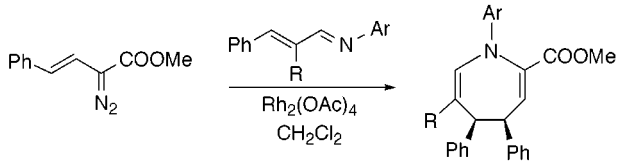
Received September 5, 2001

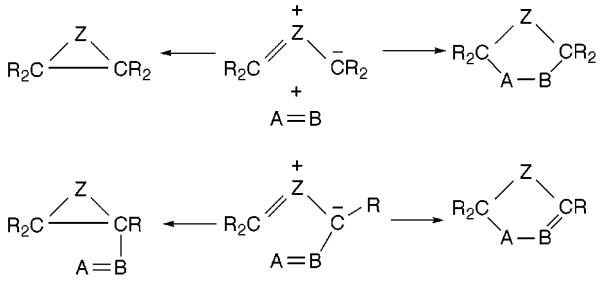
ABSTRACT



Styryldiazoacetates are effective reactants for ylide formation that results in the formation of dihydropyrroles and dihydroazepines with high stereocontrol and in high yields.

The chemistry of carbonyl ylides is an area of continuing interest, especially when their generation occurs by catalytic decomposition of diazo compounds,[1−3] and similar processes of imminium (azomethine) ylides have long been important for the construction of heterocyclic compounds.[4,5] Ylide reactions occur via mechanistically well-defined intermolecular or intramolecular cycloaddition processes (Scheme 1), and these transformations are well-entrenched in organic methodologies. Less well-known are electrocyclic reactions of ylide intermediates, and they are virtually nonexistent for ylides derived from diazocarbonyl compounds.[6,7]

Scheme 1



However, we recently reported stereospecific ring closure of phenyldiazoacetate-derived carbonyl and imminium ylides

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(3) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998, Chapter 7. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(4) (a) Zecchi, G. *Synthesis* **1991**, 181. (b) Marx, K.; Eberbach, W. *Tetrahedron* **1997**, *53*, 14687. (c) Clark, R. B.; Pearson, W. H. *Org. Lett.* **1999**, *1*, 349.

(5) (a) Arany, A.; Bendell, D.; Groundwater, P. W.; Garnett, T.; Nyerges, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2605. (b) Noguchi, M.; Yamada, H.; Takamura, S.; Uchida, T.; Hironaka, M.; Kakehi, A.; Yamamoto, H. *Eur. J. Org. Chem.* **2000**, 1489.

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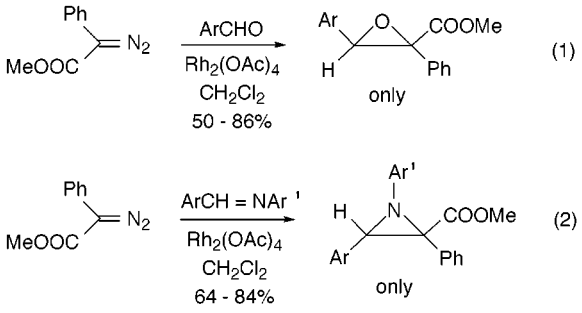
(7) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210.

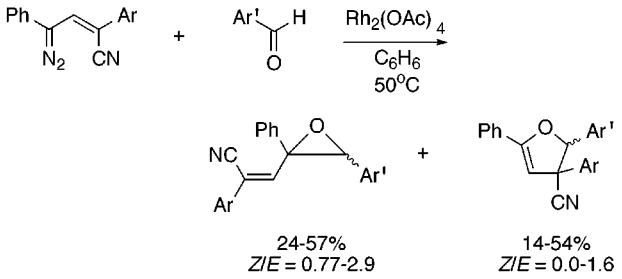
10.1021/ol016703i CCC: $20.00
Published on Web 10/19/2001

to form epoxides and aziridines, respectively, in high yield.[8] Rhodium(II) acetate catalyzed reactions of phenyldiazoacetate with an equivalent amount of aldehydes produced (*Z*)-epoxides as the sole reaction products (eq 1), whereas



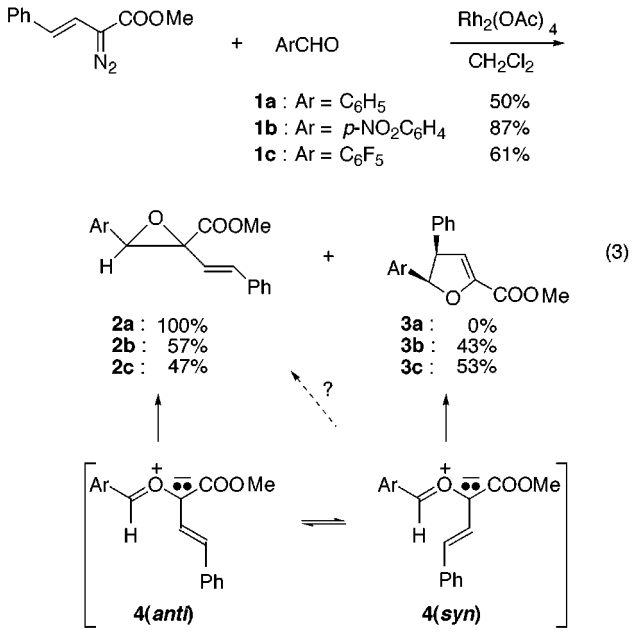
with an equivalent amount of imine the sole product was the (*E*)-configured aziridine. Epoxidation occurred even when extended conjugation, with cinnamaldehydes and/or styryldiazoacetates, would have allowed the formation of five- or seven-membered rings. Given the facility with which these reactions occur and their apparent stereospecificity, we have continued our investigations. Prompted by a recent report that both dihydrofurans and oxiranes are formed nonstereospecifically from vinylcarbonyl ylides (Scheme 2),[9] we

Scheme 2



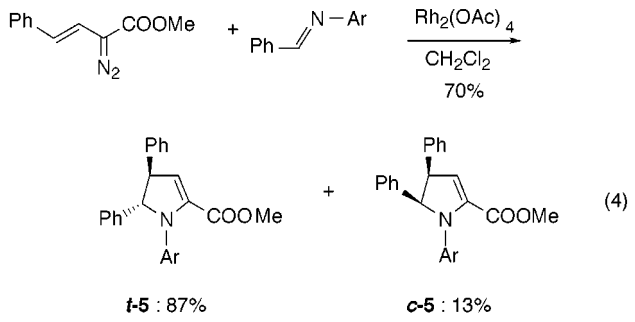
now report the extension of ylide transformations with styryldiazoacetates to five- and seven-membered ring heterocycles with high or complete stereocontrol.[10]

The first indication of the extension of this methodology beyond epoxidation and aziridation occurred in the reaction of methyl styryldiazoacetate with *p*-nitrobenzaldehyde, in which case 43% of the reaction products was dihydrofuran **3** having only the *cis* stereochemistry, as determined by NOE (eq 3). Here a pronounced electronic effect that allows leakage of the intermediate ylide to the dihydrofuran would seem to be operative. In agreement, use of 2,4-dinitrobenzaldehyde gave **2**:**3** in a 33:67 ratio (71% yield). Control experiments established that **3** did not arise from **2** under



the reaction conditions. Thus, increasing electron withdrawal from the carbonyl group directed product formation to dihydrofuran **3** in preference to oxirane **2** presumably through carbonyl ylide intermediates **4** (*syn* and *anti*). When the catalyst used was the chiral dirhodium(II) tetrakis[methyl 4(*S*)-azetidinonecarboxylate], $Rh_2(4S\text{-MEAZ})_4$,[11] reaction of methyl styryldiazoacetate with *p*-nitrobenzaldehyde gave oxirane and dihydrofuran products **2b**:**3b** in a ratio of 70:30, which was considerably different from the ratio of the same products formed with $Rh_2(OAc)_4$ catalysis.

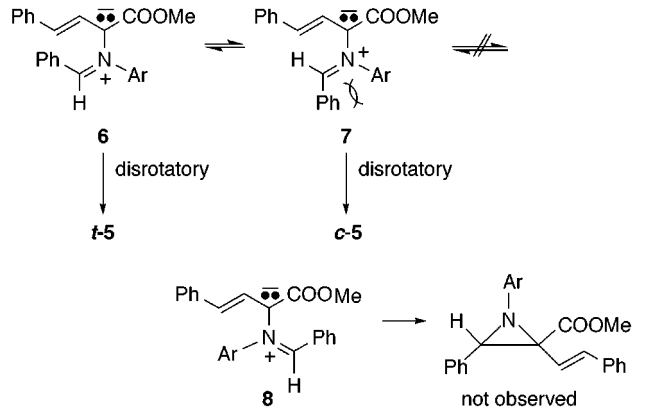
In contrast to results with aldehydes, those with benzalanilines give only dihydropyrroles (eq 4, Ar = *p*-$NO_2C_6H_4$).



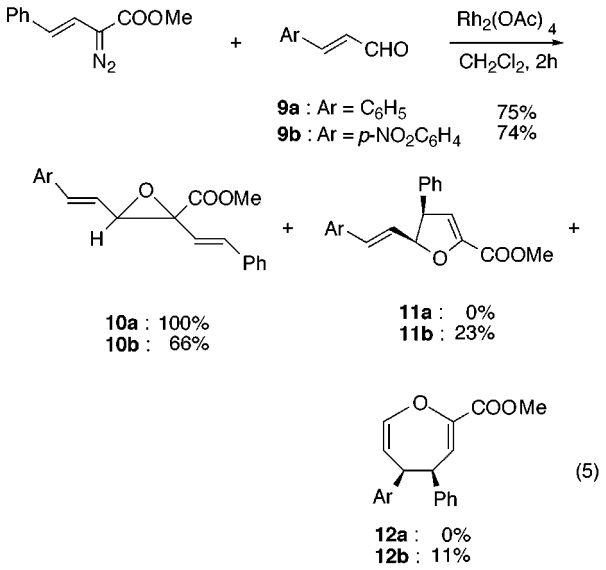
Here both *cis* and *trans* isomers of **5** are observed, but the *trans* isomer is, by far, in excess over the *cis* isomer. These results and those with benzaldehyde are consistent with the preferred structures of the intermediate ylides and their electrophilic reactions. Thus, for example, the higher yield of ***t*-5** is likely to be a result of the preference for **6** over **7** (Scheme 3), and the absence of aziridine product is seen to be a result of the relative absence of ylide **8** as a result of steric preferences. That only the *cis* isomer of **3** is formed in the carbonyl ylide transformation is assumed to be due to the absence of the intermediate geometry analogous to **6**.

(8) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933.
(9) Hamaguchi, M.; Matsubara, H.; Nagai, T. *J. Org. Chem.* **2001**, *66*, 5395.
(10) There are earlier reports of dihydrofuran formation from vinylcarbonyl ylides: (a) Anac, O.; Dant, A. *Liebigs Ann./Recl.* **1997**, 1249. (b) Spencer, T. A.; Villarica, D. L.; Storm, D. L.; Weaver, T. D.; Friary, R. J.; Posler, J.; Shafer, P. R. *J. Am. Chem. Soc.* **1967**, *89*, 5497.
(11) Doyle, M. P.; Davies, S. B.; Hu, W. *Org. Lett.* **2000**, *2*, 1145.

Scheme 3



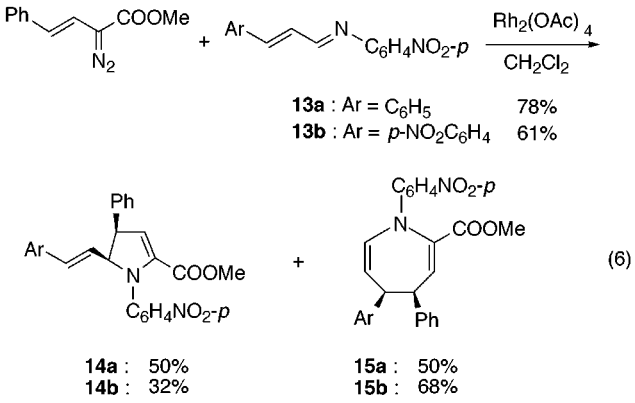
Extending conjugation in the intermediate ylide allowed access to seven-membered ring heterocycles. As anticipated from results described in eq 3, reaction of styryldiazoacetate with *p*-nitrocinnamaldehyde gave a mixture of products in which oxirane **10**, dihydrofuran **11**, and oxepine **12** were formed in competition (eq 5). For each, only one stereoisomer



was formed (≥20:1). In reactions of methyl phenyldiazoacetate with cinnamaldehyde only oxirane **10a** was obtained, indicating once again the existence of a pronounced electronic effect.

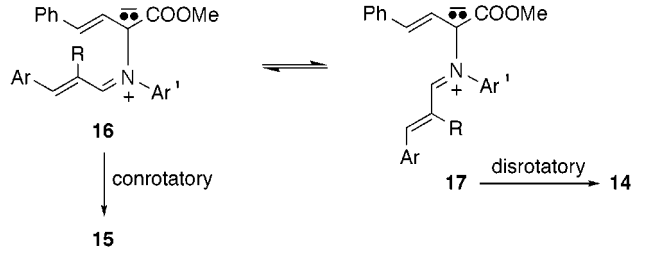
To ascertain the cause of formation of **11** and **12**, the reaction of methyl stryryldiazoacetate with *p*-nitrocinnamaldehyde was investigated in greater detail using different catalysts and various reaction conditions. At a reaction time of 1 h, **12b** was virtually absent, but there was a measurable amount of **11b** [e.g., 74% **10b**, 22% **11b**, 4% **12b** using Rh_2(4*S*-MEAZ)$_4$, and 82% **10b**, 16% **11b**, and 2% **12b** using Davies' Rh_2(*S*-DOSP)$_4$ catalyst].[12] When isolated **10b** was heated at reflux in dichloromethane, there was complete and quantitative conversion to **11b** and **12b** within 24 h (57% **11b**, 43% **12b**), and the presence or absence of rhodium(II) acetate had no influence on this transformation (rate or product selectivity). Furthermore, **11b** and **12b** were not interconvertable under the same conditions, the composite results indicating that **10b** was transformed to an intermediate ylide from which both **11b** and **12b** were produced (thermodynamic control) but that the initially formed ylide provided both **10b** and **11b** (kinetic control).

With imines derived from cinnamaldehydes, catalytic reactions with styryldiazoacetate resulted in a mixture of dihydropyrroles **14** and dihydroazepines **15**, each as only one stereoisomer (eq 6). As with eq 4 no trace of aziridine



product was evident. These results are consistent with the preferred structures of the intermediate ylides and with their electrocyclic reactions (Scheme 4).

Scheme 4



The absence of the *trans* isomer for **14** corresponds to a regiospecific conversion of **16** into **15**, and of course, **14** can only be formed from **17**. Whether or not **14** and **15** are generated by initial aziridine formation followed by its conversion to **14** and **15** could not be ascertained, as it was for dihydrofuran and oxepines formed from cinnamaldehydes (eq 5).

The distribution of product between **14** and **15** was invariant with catalyst but could be modified substantially by the presence of a methyl group at the 3-position of the reacting imine. We reasoned that this structural modification would decrease the stability of **17** relative to **16**. In this case the sole product, formed in 73% isolated yield, was dihy-

(12) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

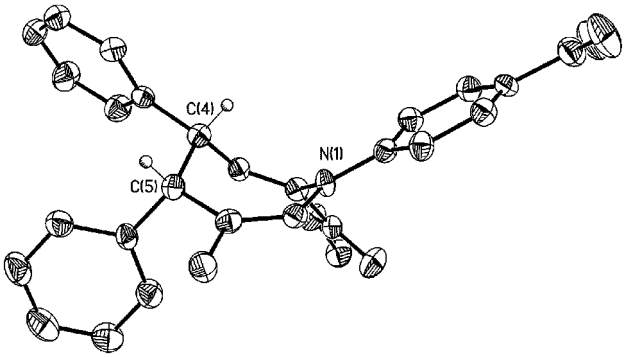
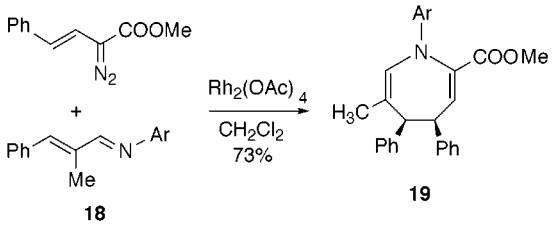


Figure 1. Crystal structure of **19** (Ar = *p*-$NO_2C_6H_4$) with selected bond lengths [Å] and angles [deg]: N1−C7 1.410(5), N1−C2 1.428(5), C2−C3 1.325(5), C3−C4 1.496(5), C4−C5 1.565(5), C5−C6 1.511(5), C6−C7 1.329(5), C7−N1−C2 118.6(3), C3−C2−N1 120.8(4), C3−C4−C5 109.6(3), C6−C5−C4 114.2(3), C7−C6−C5 127.5(4).

droazepine **19** (eq 7, Ar = *p*-$NO_2C_6H_4$) whose X-ray crystal structure (Figure 1) confirmed this geometry.[13,14]



(7)

Several processes have been used to form azomethine ylides suitable for 1,7-electrocyclization. Noguchi and coworkers have employed acyclic and heterocyclic aldehydes and their imines bearing (alk-2-enyl)amino moieties at neighboring positions to generate azomethine ylides.[15] Butadienyl pyridinium ylides and butadienylaziridines have also been used.[16] Each involves deprotonation to reach the azomethine ylide. The concise methodology of ylide transformations, including their use in dipolar addition reactions,[17] using catalytic diazo decomposition of vinyldiazoacetates has the potential of being far more versatile than previously described processes.

Acknowledgment. We are grateful to the National Science Foundation and to the National Institutes of Health (GM 46503) for their support of this research. Professor Huw H. M. L. Davies provided us with a sample of Rh_2(*S*-DOSP)$_4$. We also acknowledge the Molecular Structure Laboratory at the University of Arizona, the NSF grant (CHE 9610374) that provided the diffractometer, and Dr. Michael Carducci for his assistance.

Supporting Information Available: Experimental procedures and product analyses, as well as crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crystal data for **19**: $C_{27}H_{24}N_2O_4$, M_r = 440.48, monoclinic, space group *P*2(1)/*n* with *a* = 11.131(2), *b* = 16.910(4), *c* = 12.432(3) Å, *b* = 109.575(4)° volume = 2204.8(8) Å^3, *Z* = 4, ρ_{calc} = 1.327 mg/m^3, *F*(000) = 928. Colorless block (0.10 × 0.17 × 0.17 mm^3). Data were collected out to 2θ = 60° by an ω-scan technique (0.2° ω scan) and an exposure time of 30 s on a Bruker SMART 1000 CCD detector X-ray diffractometer at 170(2) K using graphite Mo Kα radiation (λ = 0.71073 Å). A total of 22,795 reflections were integrated and retained, of which 4624 were unique. Of the unique reflections, 1641 (35%) were observed >2σ(*I*). Solution was achieved utilizing direct methods followed by Fourier synthesis. Hydrogen atoms were located in the difference map and given thermal parameters equal to 1.2 times U_{iso} of that bonded atom; their positions were refined. Conventional refinement indices using the 1641 reflections with F > 4σ(*F*) are R1 = 0.0591, wR2 = 0.1366. The structure was solved using SHELXS in the Bruker SHELXTL (version 5.0) software package.

(14) Crystallographic data (excluding structure factors) for **19** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-171883. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2IEZ, U.K. (fax: (+44) 1223-336-033. e-mail: deposit@ccdc.cam.ac.uk).

(15) (a) Noguchi, M.; Yamada, H.; Takamura, S.; Okada, K.; Kakehi, A.; Yamamoto, H. *Tetrahedron* **2000**, *56*, 1299. (b) Noguchi, M.; Mizukoshi, T.; Nakagawa, S.; Kakehi, A. *Tetrahedron* **1996**, *52*, 13111. (c) Noguchi, M.; Mizukoshi, T.; Uchida, T.; Kuroki, Y. *Tetrahedron* **1996**, *52*, 13097.

(16) Marx, K.; Eberbach, W. *Tetrahedron* **1997**, *53*, 14687.

(17) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595. Rigby, J. *Org. React.* **1997**, *51*, 351.