Pergamon

Tetrahedron Letters 41 (2000) 1491–1494

TETRAHEDRON LETTERS

Stereoselectivity in the rhodium(II) acetate catalysed cyclopropanations of 2-diazo-1-indanone with styrenes

William Bauta,[a,*] John Dodd,[a] James Bullington,[a] Diane Gauthier,[b] Gregory Leo [b] and Patricia McDonnell [b]

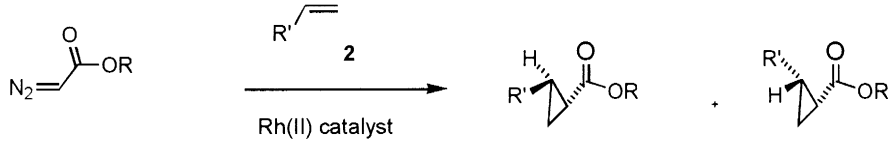
[a]*Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Route 202, Raritan, New Jersey 08869, USA*
[b]*Chemical Support, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477, USA*

Received 24 November 1999; revised 17 December 1999; accepted 19 December 1999

Abstract

The rhodium(II) acetate catalysed cyclopropanation reactions of 2-diazo-1-indanone **4** with various substituted styrenes **5** have been investigated. The cyclopropane diastereomer **6a** bearing a *trans* relationship between the carbonyl and the aryl ring was in all cases the predominant isomer and the ratio of stereosiomers almost constant over a range of styrene substituents. Styrenes bearing electron-donating substituents gave slightly better stereoselectivity in favour of the *trans* isomer. These results are substantiated by a mechanistic proposal.

The rhodium(II) catalysed cyclopropanation of olefins by α-diazocarbonyl compounds is a well-established synthetic method. The diastereoselectivity and enantioselectivity in the intermolecular cyclopropanation reactions of diazoacetates has been a subject of continuing interest.[1] Generally, the sterically larger olefin substituent (R′ in **2**) is *trans* (*anti*) to the carboxylate group in the product cyclopropanes **3**. This selectivity can be increased by choosing the right catalyst[2] or by adding sterically larger R and R′ groups on the diazoacetate **1** and the olefin **2,** respectively.[1a]



1 **3a** **3b**

In contrast to diazoacetates, there is considerably less data on the intermolecular cyclopropanation stereoselectivity of diazoketones under rhodium catalysis. In connection with an SAR development

* Corresponding author. Current address: Ilex Oncology, Inc., 14785 Omicron Drive, Suite 201, San Antonio, TX 78245, USA.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00002-2

program, we required access to cyclopropanes of type **6**. We report here our results on the stereoselectivity of the rhodium(II) acetate catalysed cyclopropanation of various styrenes **5** with 2-diazo-1-indanone **4** to give cyclopropanes **6** (Table 1).[3]

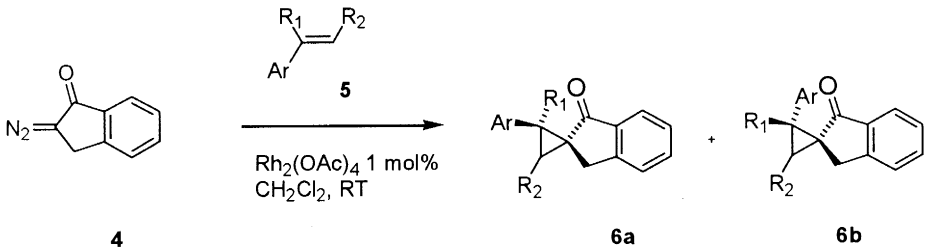


Table 1
Reactions of diazoketone **4** with olefins to give cyclopropanes **6**[a]

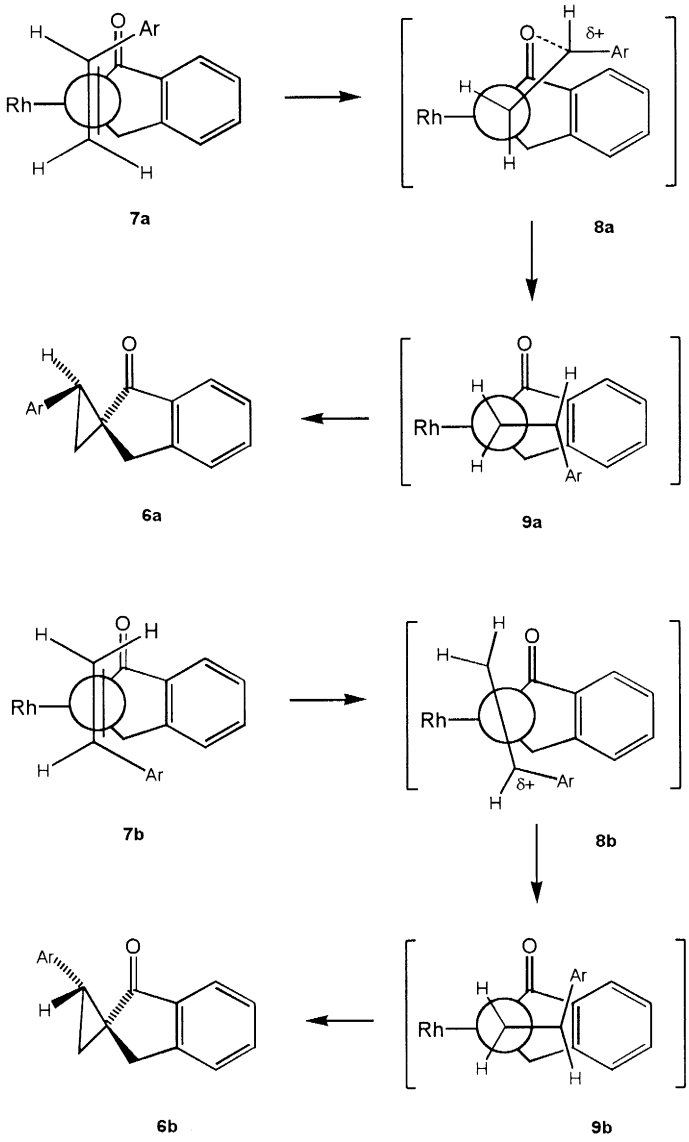
		Styrene **5**		Isolated Yield (%)[b]		Crude Ratio[c]
Entry	**Ar**	**R_1**	**R_2**	**6a**	**6b**	**6a:6b**
1	Ph	H	H	36	7	3.2:1
2	4-OMeC_6H_4	H	H	53	23	3.1:1
3	3,4-(OMe)2C_6H_4	H	H	52	20	3.2:1
4	3,4,5-(OMe)C_6H	H	H	46	16	3.3:1
5	4-BrC_6H_4	H	H	28	7	2.0:1
6	4-ClC_6H_4	H	H	30	5	2.2:1
7	4-FC_6H_4	H	H	46	15	2.1:1
8	4-OAcC_6H_4	H	H	35	15	1.8:1
9	2,4,6-MeC_6H_4	H	H	31	8	3.0:1
10	Ph	Me	H	60	18	3.3:1
11	3-OMe-C_6H_4	H	H	50	12	3.3:1
12	3-F-C_6H_4	H	H	40	13	2.9:1
13	3-Cl-C_6H_4	H	H	29	10	3.3:1
14	Ph	Ph	H	69	---	---
15	Ph	t-Bu	H	0	0	---
16	3-$NO_2C_6H_4$	H	H	0	0	---
17	Ph	H	Me	0	0	---

[a] Procedure as given in text. [b] Isolation by silica gel chromatography using hexane and ethyl acetate as eluent. [c] Ratio determined by integration of proton NMR spectum of crude reaction mixtures after removal of most of the styrene by Kugelrohr distillation.

Diazoketone **4** was prepared from the corresponding oxime by a Forester reaction.[4] Cyclopropanations were conducted by dropwise addition of **4** (1 equiv.) in CH_2Cl_2 over 20 min to a well-stirred CH_2Cl_2 solution of the styrene **5** (10 equiv.) and $Rh_2(OAc)_4$ (0.01 equiv.) at room temperature. Solvent was removed after 2 h. The resulting product mixtures consisted of two cyclopropane isomers (**6a** and **6b**), unreacted styrene **5**, and polar baseline materials, which were not, characterised (Table 1). Product ratios were determined by proton NMR analysis of the crude reaction mixtures and the isomers separated by chromatography on silica gel. Product stereochemistries were assigned according to the NOESY spectra of the purified isomers.

Diazoketone **4** presents a conformationally rigid framework with only a small steric difference between substituents on the carbene carbon. Over a range of electron-donating (entries 2,3,4), electron-withdrawing (entries 5–8) and hydrogen (entry 1) substituents on the styrene ring, the stereoselectivity of the reaction was between 2:1 and 3:1. The *trans* (*anti*) relationship between the aromatic ring and carbonyl was in all cases predominant. Likewise, the sterically more demanding 2,4,6-trimethylstyrene (entry 9) and α-methyl styrene (entry 10) did not significantly affect the stereoselectivity. Interestingly,

the more electron-poor styrenes (entries 5–8) gave rise to slightly worse stereoselectivity (2:1 vs 3:1) 3-nitrostyrene failed to give cyclopropane product as did β-methylstyrene and *t*-butylstyrene (entries 15–17). Good reactivity was observed with 1,1-diphenylstyrene which gave only 1 isomer (entry 14).



Doyle has proposed a mechanistic model to account for the predominance of *trans* stereoisomers in the cyclopropanations of diazoacetates and related diazo compounds.[5] Applying this idea to the case of diazoketone **4** suggests that stereoisomeric pi-complexes **7a** and **7b** are reversibly formed, the aryl group favouring an orientation away from the bulky metal, leading, respectively, to transition states **9a** and **9b**. The preference for *trans* stereochemistry presumably arises due to stabilisation of the developing positive charge at the benzylic carbon by the carbonyl group as the transition state geometry is approached (**8a** vs **8b**). This stabilisation can occur in **8a** but not in the case of **8b**. The slight decrease in stereoselectivity observed in the case of halogen and acetoxy-substituted styrenes would imply a decrease in positive charge at the benzylic carbon (greater double bond character) as the transition state geometry

is approached, making the stabilising effect of the carbonyl in **8a** less pronounced. The opposite is true for substituents, which stabilise the benzylic cation. The fact that the stereoselectivities for **4** are greater than is observed for styrene and ethyl diazoacetate with rhodium(II) acetate (*cis*/*trans*=1.6)[2a] may be accounted for by the greater electron density of the ketone carbonyl in **8a** compared to the ester. The present results are thus generally consistent with the Doyle interpretation.

References

1. (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. (b) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919. (c) Loffler, F.; Hagen, M.; Luning, U. *Synlett* **1999**, 1826. (d) Kolotuchin, S. V.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 7921. (e) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (f) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapter 5.1. Reissig, H.-U. In *Stereoselective Synthesis of Houben–Weyl Methods of Organic Chemistry*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: New York, 1995; Vol. E21c. (g) Doyle, M. P.; McKervey, M. A. *Chem. Commun.* **1997,** *11*, 983.
2. (a) Doyle, M. P.; Loh, K.-L.; DeVries, K. M.; Chinn, M. S. *Tetrahedron Lett*. **1987**, *28*, 833. (b) Xu, Y.; Wang, Z. Y.; You, T. P. *Chin. Chem. Lett.* **1998**, *9*, 607. (c) Endres, A.; Maas, G. *Tetrahedron Lett.* **1999**, *40*, 6365.
3. Shechter and co-workers have reported the rhodium acetate catalysed reaction of **4** with styrene in toluene from which they isolated a single cyclopropane of undetermined stereochemistry in 59% yield. Rosenfeld, M. J.; Ravi Shankar, B. K.; Schechter, H. *J. Org. Chem.* **1988**, *53*, 2699.
4. Horner, L.; Kirmse, W.; Muth, K. *Chem. Ber.* **1958**, *91*, 430.
5. Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.