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Stereoselectivity of Methyl Aryldiazoacetate Cyclopropanations of 1,1-Diarylethylene. Asymmetric Synthesis of a Cyclopropyl Analogue of Tamoxifen

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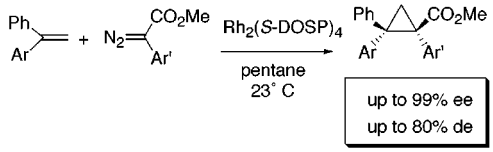
ABSTRACT



Dirhodium tetrakis(*S*-(*N*-dodecylbenzenesulfonyl)prolinate) (Rh_2(*S*-DOSP)$_4$)-catalyzed decomposition of methyl phenyldiazoacetate in the presence of 1,1-diarylethylenes results in intermolecular cyclopropanation with high enantioselectivity (up to 99% ee) and moderate diastereoselectivity (up to 80% de). The reaction was applied to the asymmetric synthesis of a cyclopropyl analogue of tamoxifen.

Tamoxifen **1** is a very effective medication for the treatment and possible prevention of breast cancer (Figure 1).[1] Due to its useful therapeutic properties, the synthesis and biological evaluation of numerous analogues of tamoxifen have been described.[2] These have included various triarylcyclopropanes;[3] however, the cyclopropyl analogue **2** of tamoxifen has not been reported. In this paper, we describe the synthesis of enantiomerically pure **2** by means of an asymmetric cyclopropanation of 1,1-diarylethylenes.

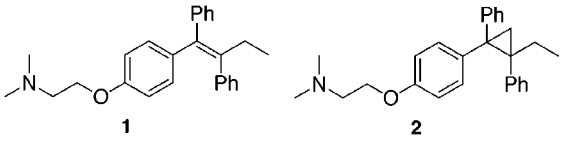
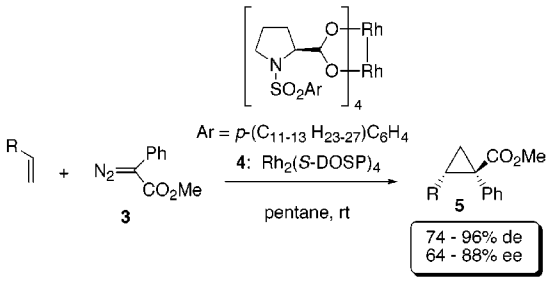


Figure 1. Tamoxifen (**1**) and tamoxifen analogue **2**.

The background behind this current study was the discovery that the decomposition of methyl phenyldiazoacetate (**3**) by dirhodium tetraprolinates such as Rh_2(*S*-DOSP)$_4$ (**4**)[4] in the presence of alkenes results in highly enantioselective and diastereoselective intermolecular cyclopropanations to form **5** (Scheme 1).[5] Furthermore, it has been shown that

Scheme 1



(1) (a) Crommentuyn, K. M. L.; Schellens, J. H. M.; Vandenberg, J. D.; Beijnen, J. H. *Cancer Treat. Rev.* **1998**, *24*, 345. (b) White, I. N. *Carcinogenesis* **1999**, *20*, 1153. (c) Jordan, V. C.; Morrow, M. *Endocrine Rev.* **1999**, *20*, 253. (d) Furr, B. J. A.; Jordan, V. C. *Pharmacol. Ther.* **1984**, *25*, 127.

(2) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1999**, *99*, 723.

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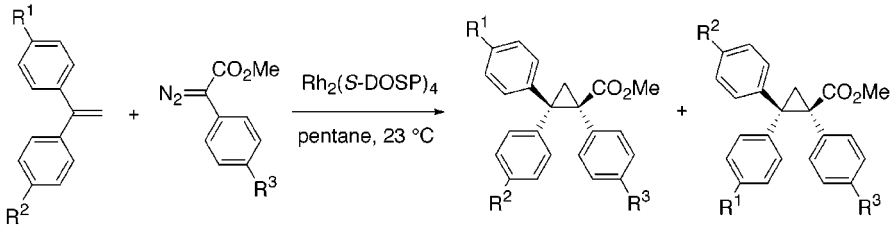
Table 1. Stereoselectivity of Methyl Aryldiazoacetate Cyclopropanations of 1,1-Diarylethylenes



6 7

entry	R^1	R^2	R^3	product	yield, %	ratio **6**:**7**	**6**, % ee	**7**, % ee
1[a]	H	H	H	**a**	87		97	
2	NO_2	H	H	**b**	90	55:45	95	91
3	H	OMe	H	**c**	84	87:13	99	96
4[b]	H	NHAc	H	**d**	75	76:24	92	88
5[b]	NO_2	OMe	H	**e**	80	88:12	93	74
6	H	OMe	Cl	**f**	94	89:11	99	95
7	H	OMe	OMe	**g**	84	90:10	98	94

[a] For a similar reaction using Rh_2(*S*-TBSP)$_4$ as catalyst, see ref 6. [b] Solvent was pentane/CH_2Cl_2.

exceptionally high levels of enantioselectivity (97% ee) are obtained when 1,1-diphenylethylene is the substrate for these cyclopropanations.[6] To extend this reaction to the synthesis of the tamoxifen analogue **2**, unsymmetrical 1,1-diarylethylenes would need to be used, and therefore, issues of diastereoselectivity in addition to enantioselectivity would need to be addressed.

To evaluate the stereochemical issues of this chemistry, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of methyl aryldiazoacetates with a series of 1,1-diarylethylenes was examined and the results are summarized in Table 1. For most of the reactions, pentane was used as the solvent, because it has been found to give the highest enantioselectivity in Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanations between **3** and styrene.[5] For 1-(4-acetamidophenyl)-1-phenylethylene and 1-(4-methoxyphenyl)-1-(4-nitrophenyl)ethylene, pentane/CH_2Cl_2 was used as solvent due to their poor solubility in pentane.

The first group of reactions was carried out using methyl phenyldiazoacetate (**3**) as the carbenoid precursor (entries 1−5), so that the effect of modifications to the 1,1-diarylethylene could be determined.[7] A very interesting effect of electron-donating substituents on the diastereoselectivity of these reactions was observed. Even though the reaction of 1-(4-nitrophenyl)-1-phenylethylene gave essentially a 1:1 mixture of diastereomers (dr = 55:45, entry 2), the reaction with 1-(4-methoxyphenyl)-1-phenylethylene was considerably more diastereoselective, resulting in a 87:13 mixture of **6c** and **7c** (entry 3). Similar effects were seen with 1-(4-acetamidophenyl)-1-phenylethylene (dr = 76:24, entry 4) and also with 1-(4-methoxyphenyl)-1-(4-nitrophenyl)ethylene (dr = 88:12, entry 5).

To study the electronic effects of the aryl group in the carbenoid intermediate on the diastereoselectivity, (4-chlorophenyl)diazoacetate and (4-methoxyphenyl)diazoacetate were tried next (entries 6 and 7). The diastereoselectivity and enantioselectivity obtained with these substrates were virtually the same as was obtained with methyl phenyldiazoacetate (entry 3).

The enantioselectivity of the cyclopropanation was found to be good to excellent. Especially, high ee's (98−99% ee) were observed for the major diastereomer derived from 1-(4-methoxyphenyl)-1-phenylethylene (entries 3, 6, and 7). The ee's were found to be slightly lower with 1-(4-acetamidophenyl)-1-phenylethylene (92% ee, entry 4) and 1-(4-methoxyphenyl)-1-(4-nitrophenyl)ethylene (93% ee, entry 5). This is probably because CH_2Cl_2/pentane was used as solvent with these substrates, as polar solvents lower the enantioselectivity in Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of styrene with aryldiazoacetates.[8]

To probe further the cause of the diastereoselectivity of these reactions, the reactions between methyl phenyldiazoacetate and 1-[4-(2-chloroethoxy)phenyl]-1-phenylethylene **8** were conducted using several rhodium(II) catalysts in CH_2Cl_2 (Table 2). In the case of $Rh_2(OAc)_4$, a fairly moderate diastereoselectivity (64:36) was obtained, favoring **9-E** (entry 1). The diastereoselectivity was slightly improved with the more electron deficient catalyst $Rh_2(TFA)_4$ (70:30, entry 2)

(3) (a) Abidi, S. M. A.; Howard, E. W.; Dmytryk, J. J.; Pent, J. T. *Clin. Exp. Metathesis* **1998**, *16*, 235. (b) Rajah, T. T.; Dunn, S. T.; Pento, J. T. *Anticancer Res.* **1996**, *16*, 837. (c) Jain, P. T.; Pento, J. T.; Magarian, R. A. *Cancer Chemother. Pharmacol.* **1996**, *38*, 238. (d) Day, B. W.; Magarian, R. A.; Jain, P. T.; Pento, J. T.; Mousissian, G. K.; Meyer, K. L. *J. Med. Chem.* **1991**, *34*, 842. (e) Bedford, G. R.; Walpole, A. L.; Wright, B. *J. Med. Chem.* **1974**, *17*, 147.

(4) (a) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107. (b) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459.

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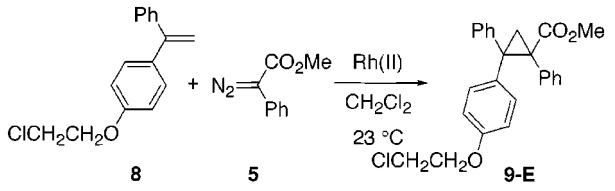
(6) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; Garcia, C. F.. *Tetrahedron Lett.* **1996**, *37*, 4129

(7) The relative configuration of **6** and **7** was determined by NOE. The absolute configuration is tentatively assigned by analogy to related reactions, see ref 4 and Moye-Sherman, D.; Welch, M. B.; Reibenspies, J.; Burgess, K. *J. Chem. Soc., Chem. Commun.* **1998**, 2377.

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

Table 2. Effect of Catalyst on Diastereoselectivity



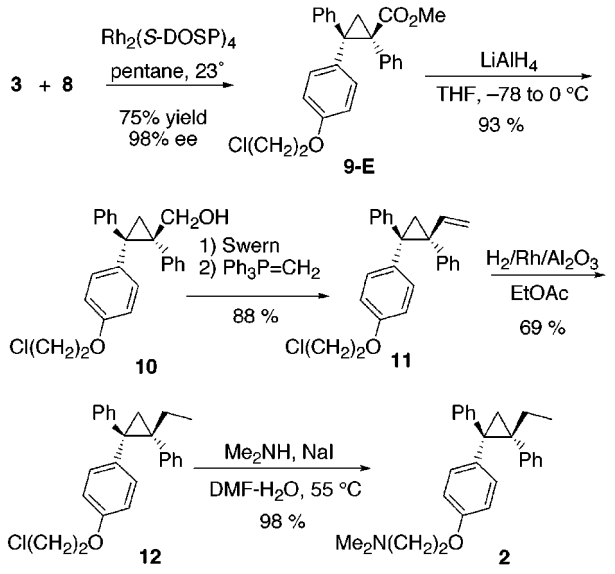
+ Z isomer

entry	Rh(II) catalyst	E/Z ratio
1	$Rh_2(OAc)_4$	64 : 36
2	$Rh_2(TFA)_4$	70 : 30
3	$Rh_2(TPA)_4$	80 : 20
4	Rh_2(*S*-DOSP)$_4$	84 : 16

and with the more sterically demanding catalyst Rh_2(triphenylacetate)$_4$ (80:20, entry 3). The highest diastereoselectivity (87:13, 89% combined yield) was obtained using Rh_2(*S*-DOSP)$_4$, which is more electron deficient and sterically demanding than $Rh_2(OAc)_4$. Furthermore, with Rh_2(*S*-DOSP)$_4$ in pentane, **9-E** was obtained in 98% ee and 75% isolated yield after preparative thin-layer chromatography.

Cyclopropane **9-E** was readily converted to tamoxifen analogue **2** as illustrated in Scheme 2. The methyl ester in **9-E** was reduced by $LiAlH_4$ to give alcohol **10** in 93% yield. The alcohol was oxidized under Swern conditions to give the corresponding aldehyde; however, since the aldehyde was unstable to purification by chromatography on SiO_2, the crude product was immediately treated with $Ph_3P{=}CH_2$ to give alkene **11** in 88% yield (two steps). Hydrogenation of

Scheme 2



11 with Rh/Al_2O_3 gave ethylcyclopropane **12** in 69% yield. The primary chloride in **12** was readily displaced by Me_2-NH in the presence of NaI in DMF$-H_2O$ at 55 °C to give **2** in 98% yield, which was further purified as its hydrochloride salt by recrystallization from EtOAc. The other enantiomer of **2** was prepared in the same way from the enantiomer of **9-E** that was obtained using Rh_2(*R*-DOSP)$_4$ as catalyst.

The high enantioselectivity observed in these cyclopropanations further demonstrates the synthetic utility of Rh_2(*S*-DOSP)$_4$ as a chiral catalyst. The reasonable diastereoselectivity of these cyclopropanations is intriguing because the diastereocontrol is caused by the distant para substituents on the aryl rings. Previously, we reported highly diastereoselective cyclopropanation reactions between phenyldiazoacetate and styrenes (>30:1 *E*/*Z* ratios) catalyzed by Rh_2(*S*-DOSP)$_4$.[5] On the basis of the configuration of the major diastereomer, a hypothetical model to explain the formation of the major diastereomer was suggested as **13** in Figure 2.[4,5] In this model, the C=C bond in styrene approaches side-

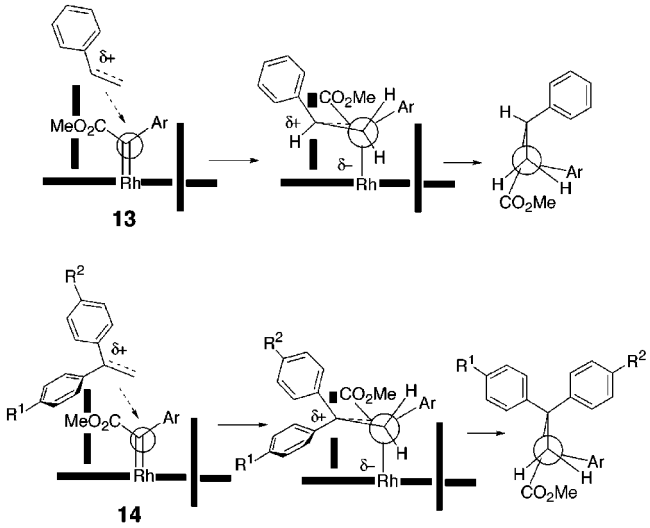


Figure 2. Models for stereocontrol.

on from the ester side, forming a partial positive charge α to the phenyl group. Our recent Hammet study on cyclopropanation reactions between methyl aryldiazoacetate and various 4-substituted styrenes also suggests that considerable positive charge is built up at the α carbon of styrene during these cyclopropanations.[9]

Our current hypothetical model to explain the formation of the major diastereomer in cyclopropanation with 1,1-diarylethylenes is analogous to model **13** and is shown as **14** in Figure 2. In this model, the C=C bond in the 1,1-diarylethylene approaches in a similar way to styrene. Both aryl groups in 1,1-diaryethylenes cannot be coplanar due to steric reasons. To minimize the steric interaction from the ligand on rhodium, the aryl group closer to the ligand prefers

(9) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, in press.

a conformation in which the aryl group and the C═C bond are orthogonal rather than coplanar. On the other hand, the aryl group that is far from the ligand may rotate more freely, so that the aryl group maintains conjugation with the C═C bond. This model is consistent with the observation that 1,1-diarylethylene with an electron-donating group at the para position of the phenyl group (methoxy, 2-chloroethoxy, and NHAc) gave moderate to good diastereoselectivity. According to model **14**, an electron-donating group at the R^2 position would stabilize the partial positive charge more effectively through conjugation rather than would one at R^1, thus accounting for the energy difference between the diastereomeric transition states. Curiously, an electron-withdrawing group on the aromatic ring has much less of an effect on the diastereoselectivity than an electron-donating group.[10]

A related electronic effect has been reported by Corey and Helal during studies on highly enantioselective CBS reduction of 4-methoxy-4′-nitrobenzophenone.[11] They suggested a model in which the 4-methoxyphenyl group and the carbonyl group are in the same plane to stabilize the Lewis acid−base interaction, while the 4-nitrophenyl group and the carbonyl group are orthogonal with the substituent on the boron to minimize the steric repulsion.

In summary, Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of aryldiazoacetates in the presence of unsymmetrical 1,1-diarylethylenes was found to give cyclopropanation products with high enantiomeric excesses. The diastereoselectivity was influenced by the electronic properties of the substituents on the 1,1-diarylethylene. Electron-donating groups such as alkoxy gave good diastereoselectivity. The synthetic utility of this cyclopropanation was demonstrated by the synthesis of both enantiomers of the cyclopropyl analogue of tamoxifen **2**. Further studies are in progress to evaluate the biological activity of these new tamoxifen analogues.

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Supporting Information Available: Full experimental data for compounds **2**, **6**, **7**, and **10**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A possible explanation for this difference in effect may come from Hammet studies we have carried out for competition reactions of substituted styrenes with various carbenoids (ref 9). In these studies, we found that vinyldiazoacetates and phenyldiazoacetates (in contrast to simple diazoacetates) display considerable selectivity in competition studies with various styrenes and the reactivity correlates well with a $\sigma+$ scale rather than a σ scale. This would suggest that the benzylic carbon of the styrene has some carbocation character in the transition state of the cyclopropanation and is stabilized by resonance through to the aromatic substituent. Consequently, it is reasonable that the methoxy group would have a more significant effect on the diastereoselectivity of the 1,1-diarylethylene cyclopropanation than a nitro group. The influence of the nitro group would be primarily through a polar effect rather than a resonance effect and would be largely independent of aromatic ring orientation. For a general discussion, see: Hine, J. In *Structural Effects on Equilibra in Organic Chemistry*; John Wiley & Sons: New York, 1975; pp 55−105.

(11) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153.