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Stereoselective synthesis of epoxides by reaction of donor/acceptor-substituted carbenoids with α , β -unsaturated aldehydes

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Abstract—The reaction of donor/acceptor-substituted carbenoids with α,β -unsaturated aldehydes results in the highly diastereoselective synthesis of epoxides. © 2001 Published by Elsevier Science Ltd.

The metal-catalyzed decomposition of diazocarbonyl compounds is a very useful transformation in organic synthesis.1 Traditionally, unsubstituted diazoacetates have been most commonly used, but in recent years it has become recognized that the diazoacetate structure has a profound effect on the reaction outcome.¹ Most notably, diazoacetates functionalized with a potentially electron donating group that would stabilize the resulting metal-carbenoid, such as vinyl,² aryl,³ heteroaryl⁴ or alkynyl,⁵ exhibit very different reactivity compared to the unsubstituted diazoacetates. Metal-catalyzed intermolecular cyclopropanations with these donor/acceptor-substituted carbenoids are routinely highly diastereoselective and chemoselective.⁶ These carbenoids are less prone to dimerization than simple diazoacetates. Aryldiazoacetates, in particular, are excellent reagents for catalytic asymmetric intermolecular C-H insertions.⁷ Prompted by a recent report⁸ that the epoxidation chemistry of methyl phenyldiazoacetate and methyl styryldiazoacetate is different from that of simple diazoacetates, we describe herein our extensive studies on the reaction of aryl-, heteroaryl- and vinyldiazoacetates with α,β -unsaturated aldehydes. These studies confirm that the reaction of donor/acceptorsubstituted carbenoids with α,β -unsaturated aldehydes is a very general and stereoselective method for the synthesis of trisubstituted epoxides (Eq. (1)).

$$\begin{array}{c} N^{2} \\ R^{1} \\ \hline CO_{2}Me \end{array} + \begin{array}{c} H \\ R^{2} \\ \hline CO_{2}Me \end{array} + \begin{array}{c} H \\ R^{2} \\ \hline CO_{2}Me \end{array} + \begin{array}{c} O \\ R^{2} \\ \hline CO_{2}Me \end{array}$$
(1)

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The metal-catalyzed decomposition of ethyl diazoacetate in the presence of aldehydes does not effectively form epoxides.9 Instead, dioxolanes are formed, whereby, the intermediate ylide undergoes a 1,3-diploar cycloaddition with a second equivalent of aldehyde. As recently reported,⁸ we have also found that the rhodium(II) acetate catalyzed decomposition of methyl phenyldiazoacetate in the presence of benzaldehyde results in the highly diastereoselective formation of the epoxide 1 (Eq. (2)). A particularly attractive feature of this reaction is that the epoxide that is formed is the opposite diastereomer to that which is formed in the traditional Darzen's condensation.¹⁰



The reaction is applicable to a range of α , β -unsaturated aldehydes as summarized in Table 1. Benzaldehydes, various heteroaromatic aldehydes and other α , β -unsaturated aldehydes are appropriate substrates (entries 1-11), and in all cases, a single diastereomer of the epoxide is formed.¹¹ The stereoselective epoxidation can be extended to many of the other donor/acceptor substituted carbenoids that we have developed. Electron rich or electron deficient functionality can be accommodated on the phenyldiazoacetate without any detrimental effect (entries 12-14). Also, heteroaryldiazoacetates may be utilized as illustrated in the reaction of the thiophene and indole derivatives (entries 15 and 16). In all instances, the reactions are highly diastereoselective (>94% de). An effective reaction is also possible with

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^a Reaction conditions: hexane/CH₂Cl₂, 30:1, rt, 1 h addition of diazo compound.

^b Ref. 8; reaction conditions: CH₂Cl₂, reflux.

^c Reaction conditions: CH₂Cl₂, rt, 1 h addition of diazo compound.

cyclohexenone, but in this case the epoxide 2 is formed as a 6.8:1 mixture of diastereomers (Eq. (3)).

$$\begin{array}{c} N_2 \\ Ph \\ \hline CO_2Me \end{array}^{+} \\ \hline \end{array} \begin{array}{c} Rh_2(OAc)_4 \\ \hline \end{array} \\ \hline \end{array} \begin{array}{c} Rh_2(OAc)_4 \\ \hline \end{array} \\ \hline \end{array} \begin{array}{c} O \\ CO_2Me \\ \hline \end{array} \\ \hline \end{array} \begin{array}{c} O \\ CO_2Me \\ \hline \end{array} \\ \hline \end{array}$$

No asymmetric induction in these reactions was observed when they were catalyzed by a chiral rhodium amide catalyst.⁸ We found a similar lack of asymmetric induction using $Rh_2(S\text{-}DOSP)_4$ as catalyst, which has generally been found to be an excellent chiral catalyst of aryldiazoacetate transformations.¹² These observations are indicative that ylide intermediates are initially formed and the metal catalyst is no longer connected to the ylide at the stage of the cyclization event.

Methyl styryldiazoacetate also was reported⁸ to form epoxides in the rhodium-catalyzed reaction with benzaldehyde and cinnamaldehyde. In our hands this reaction is more complex than was previously described.⁸ We found that the *cis*-dihydrofuran $4a^{13}$ is formed in addition to the epoxide 3a (Eq. (4)). The thermal rearrangement of vinylepoxides to *cis*-dihydrofurans is an established reaction^{14,15} but under rhodium-catalyzed reaction conditions, the epoxide **3** is stable. The mixture formed from the rhodium-catalyzed reaction likely arise due to competing cyclization of the ylide intermediate between epoxide formation and a 6π -electrocyclization to give the dihydrofuran.^{14,15} Illustrative examples of the scope of these reactions are shown in Table 2.

In conclusion, these studies further demonstrate that donor/acceptor substituted carbenoids display very different reactivity to the traditional carbenoids derived from unsubstituted diazoacetates. The reaction of aryl-diazoacetates and heteroaryldiazoacetates with α , β -unsaturated aldehydes is confirmed to be a general and highly diastereoselective method for the synthesis of epoxides. A similar reaction is possible with vinyldiazoacetates, although in this case the formation of dihydrofurans as side-products is observed.

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Table 2. Reaction of vinyldiazoacetates with aldehydes

	$R^{1} \xrightarrow{N_{2}} CO_{2}R^{2} + H_{R^{3}} \xrightarrow{R_{1}} R^{3} \xrightarrow{R_{1}} CO_{2}R^{2} + H_{R^{3}} \xrightarrow{R_{1}} CO_{2}R^{2} + H_{R^{1}} \xrightarrow{R_{1}} R^{3} \xrightarrow{R_{1}} CO_{2}R^{2}$				
Entry	\mathbb{R}^1	R ²	R ³	3:4 Ratio	3, Yield % ^a (lit. ^b yield %)
1	Ph	Me	Ph	2.5	55 (50)
2	Ph	Me	p-(OMe)Ph	2.0	60
3	Ph	Me	3,4-diClPh	1.8	44
4	Ph	Me	(E)-MeCH=CH	4.6	36
5	Ph	Me	(E)-PhCH=CH	3.6	65 (75)
6	CO ₂ Et	Et	Ph	1.6	60
7	CO ₂ Et	Et	(E)-MeCH=CH	2.3	58
8	CO_2Et	Et	(E)-PhCH=CH	4.6	76

^a Reaction conditions: hexane/CH₂Cl₂, 30:1, rt, 12 h addition of diazo compound.

^b Ref. 8; reaction conditions: CH₂Cl₂, reflux.

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