

Highly Chemoselective 2,4,5-Triaryl-1,3-dioxolane Formation from Intermolecular 1,3-Dipolar Addition of Carbonyl Ylide with Aryl Aldehydes

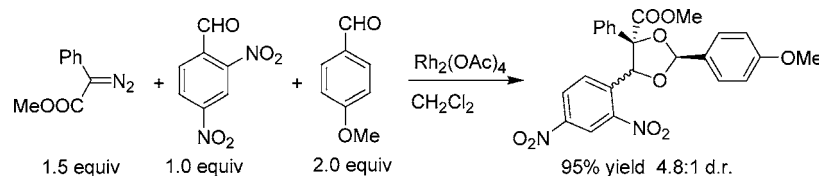
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ABSTRACT



Rhodium(II) acetate catalyzed 1,3-dipolar cycloaddition of methyl phenyldiazoacetate with a mixture of electron-rich and electron-deficient aryl aldehydes gave 1,3-dioxolanes in high yield with excellent chemoselectivity.

The catalytic generation of carbonyl ylides from diazo compounds and related reactions continue to receive a great deal of attention.¹ Among the carbonyl ylide reactions, the 1,3-dipolar cycloaddition of a carbonyl ylide^{1,2} with a suitable dipolarophile such as an alkene or alkyne forming highly substituted heterocycles is the most general reaction. In particular, intramolecular 1,3-dipolar addition reactions have been used to prepare complex synthetic targets by Padwa and others.³ In contrast, the intermolecular reactions with aldehydes or ketones have received limited attention,⁴ and most of them led to 1,3-dioxolanes.^{4a,c,d,i} Recently, the Doyle⁵ and Davies⁶ groups, respectively, reported stereospecific epoxide formation from rhodium acetate catalyzed diazo

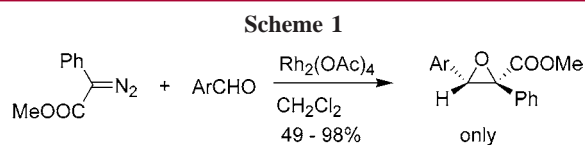
decomposition of aryldiazoacetate with aldehydes or aryl ketones. Later, a similar epoxidation process was used to prepare spiro-indoloxiranes with cyclic diazoamides by the Muthusamy group.⁷

As Doyle and Davies reported (Scheme 1), stereospecific ring closure of methyl phenyldiazoacetate-derived carbonyl ylides gave (*Z*)-epoxides as the only products in high yield without any formation of 1,3-dioxolane. To our surprise, when the reaction was performed in the presence of a mixture of an electron-rich and an electron-deficient aldehyde (**2** and **3**), 1,3-dipolar cycloaddition occurred to produce 1,3-

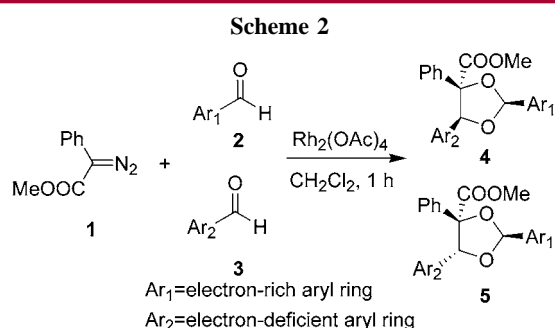
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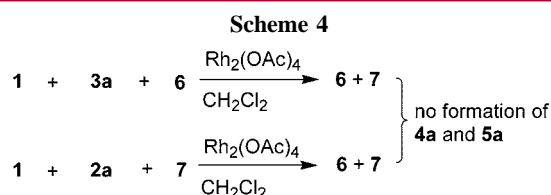
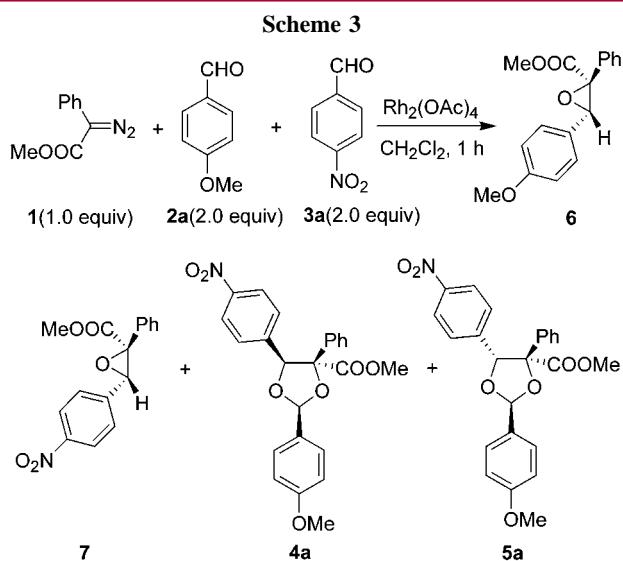
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dioxolanes as major products. Notably, only two diastereomers out of 16 possible dioxolanes were formed (Scheme 2). None of the dioxolanes derived from the diazo compound **1** with two of the same aldehydes was observed. To the best of our knowledge, this is the first example of such an intermolecular “cross” 1,3-dipolar cycloaddition reaction, in which a carbonyl ylide derived from one aldehyde selectively reacts with another aldehyde.



The first indication of this reaction occurred in the Rh₂(OAc)₄-catalyzed reaction of methyl phenyldiazoacetate with 2 equiv each of *p*-anisaldehyde and *p*-nitrobenzaldehyde to give 50% isolated yield of the dioxolanes **4a** and **5a** with 45:55 dr (Scheme 3). Epoxides **6** and **7** were formed in 13% and 11% yield, respectively, based on ¹H NMR quantitation of the crude product. The stereochemistry is reverse from the epoxidation products **6** and **7**, in which two aryl groups



are trans to each other.^{5,6} A control reaction of diazo **1** with aldehyde **3a** (**2a**) in the presence of epoxide **6** (**7**) resulted in no dioxolane formation indicating that the **4** and **5** were not formed from ring opening of the corresponding epoxides (Scheme 4).

Encouraged by the initial results, we further examined the process with the combination of various electron-rich and electron-deficient aryl aldehydes. As shown in Table 1,

Table 1. Reaction of Methyl Phenyldiazoacetate with Different Electron-Rich and Electron-Deficient Aldehydes (Scheme 2)^a

entry	Ar ₁	Ar ₂	product	yield ^b (%)	dr ^c (4/5)
1 ^d	<i>p</i> -MeOPh	<i>p</i> -NO ₂ Ph	4a + 5a	50	45:55
2 ^e	<i>p</i> -MeOPh	2,4-(NO ₂) ₂ Ph	4b + 5b	95	81:19
3 ^e	<i>o</i> -MeOPh	2,4-(NO ₂) ₂ Ph	4c + 5c	90	83:17
4 ^e	piperonyl	2,4-(NO ₂) ₂ Ph	4d + 5d	94	81:19
5 ^e	<i>m</i> -MePh	2,4-(NO ₂) ₂ Ph	4e + 5e	91	84:16
6 ^e	Ph	2,4-(NO ₂) ₂ Ph	4f + 5f	85	85:15
7 ^e	2,4-(MeO) ₂ Ph	<i>p</i> -NO ₂ Ph	4g + 5g	78	43:57
8 ^d	2,4-(MeO) ₂ Ph	<i>p</i> -NO ₂ Ph	4g + 5g	61	43:57
9 ^d	2,4,6-(MeO) ₃ Ph	<i>p</i> -NO ₂ Ph	4h + 5h	74	45:55
10 ^d	2,4,6-(MeO) ₃ Ph	<i>o</i> -NO ₂ Ph	4i + 5i	65	60:40
11 ^d	2,4,6-(MeO) ₃ Ph	Ar ₂ CHO = <i>o</i> -phthalaldehyde	4j + 5j	50	43:57
12 ^d	2,4,6-(MeO) ₃ Ph	<i>p</i> -CF ₃ Ph	4k + 5k	63	32:68
13 ^d	2,4,6-(MeO) ₃ Ph	<i>p</i> -CNPh	4l + 5l	71	40:60
14 ^d	2,4,6-(MeO) ₃ Ph	2,4-(NO ₂) ₂ Ph	4m + 5m	80	77:23

^a Reactions were performed in CH₂Cl₂ under reflux with 1.0 mol % of rhodium(II) acetate. ^b Isolated yield of products (**4** + **5**) after column chromatography purification. ^c Ratios were determined by ¹H NMR of crude reaction mixtures. ^d Substrate ratio **1/2/3** = 1:2:2 mmol. ^e Substrate ratio **1/2/3** = 1.5:2.0:1.0 mmol.

“cross” 1,3-dioxolanes were the major products, and the electron-deficient aldehydes served as dipolarophiles at all times. The reaction of a more electron-deficient dipolarophile with a carbonyl ylide derived from an electron-rich aryl

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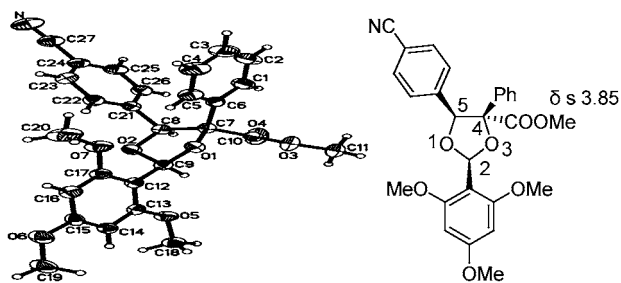


Figure 1. ORTEP representation of the crystal structure of dioxolane **4l**.

aldehyde gave dioxolanes in higher yield. For example, the combination of 2,4-dinitrobenzaldehyde and *p*-anisaldehyde provided the 1,3-dioxolane in 95% isolated yield favoring **4b** in 81:19 selectivity (entry 2). Benzaldehyde could serve as an “electron-rich” aldehyde to give successful “cross” dioxolanation in high yield (entry 6), and *o*-phthalaldehyde could serve as an “electron-deficient” aldehyde to conduct the 1,3-dipolar cycloaddition with moderate yield (entry 11).

The stereochemistry of stereoisomers **4l** and **5l** was confirmed by their X-ray structures. The perspective views of **4l** and **5l** clearly exhibit the *cis* relationship between the 2-C and the 4-C aryl rings in both isomers (Figures 1 and 2). The ¹H NMR chemical shift (δ) of 4-CO2Me in **5l** was

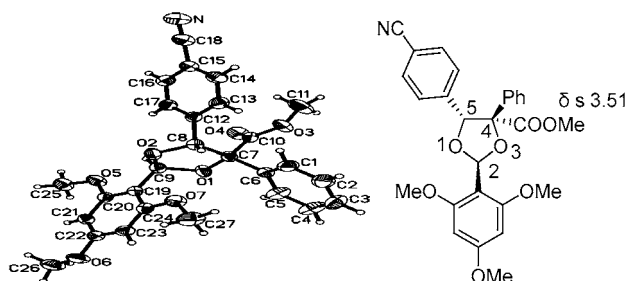
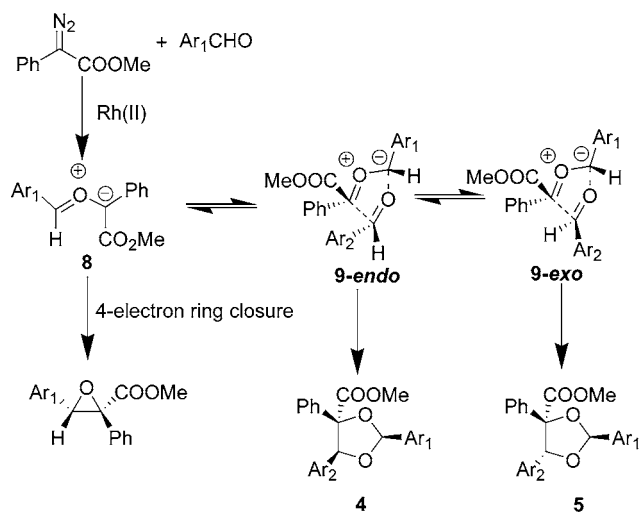


Figure 2. ORTEP representation of the crystal structure of dioxolane **5l**.

shifted to more upfield due to obvious shield from the 5-C aryl group, as can be seen in Figure 2. This diagnostic peak was used to assign the stereochemistry for other analogues.

It is interesting that the diastereoselectivity at 5-C highly depends on the electronic feature of the dipolarophile aldehyde and was less dependent on the electron-rich one. 2-Nitrobenzaldehyde and 2,4-dinitrobenzaldehyde continued to give the diastereomer favoring **4**, while other less electron-deficient aldehydes favored **5**. 2,4-Dinitrobenzaldehyde af-

Scheme 5



forded high diastereoisomeric ratios in all cases.⁸ The steric effect of ortho substitution on electron-rich aldehydes did not noticeably affect the diastereoselectivity of the products (**4/5**) (entries 2 and 3). Attempts to achieve dioxolanation from two electron-deficient aldehydes such as 2,4-dinitrobenzaldehyde with 4-nitrobenzaldehyde were unsuccessful, and epoxides were found to be major products (epoxides/dioxolanes > 10:1 from crude ¹H NMR). Complex mixtures were obtained when aliphatic aldehydes were employed as electron-rich aldehydes in this reaction.

Mechanistically, the formation of the dioxolane **4** and **5** is considered to be a dipolar cycloaddition in which the carbonyl ylide **8** generated from the carbenoid with an electron-rich aldehyde was chemospecifically trapped by another electron-deficient aldehyde (Scheme 5). The fixed *cis*-relationship between 2-C Ar₁ and 4-C Ph supports the concert process. The reason accounts for the diastereoselectivity giving different ratio of **4** to **5** is unclear. The issue deserves further investigation.

To address if ylide **8** is metal associated, the reaction of diazo compound **1** with 2,4,6-trimethoxybenzaldehyde and *p*-nitrobenzaldehyde (entry 9) was carried out with Rh₂(cap)₄ and Rh₂(*S*-DOSP)₄ individually. Preliminary results support metal-free ylide intermediate in this case. Products (**4h** + **5h**) were obtained in 41% and 45% yield, respectively, with the same ratio of **4h/5h** = 45:55 with both catalysts. The ratio was also the same as using Rh₂(OAc)₄ (entry 9). In addition, no enantioselectivity was observed in both **4h** and **5h** with the chiral catalyst Rh₂(*S*-DOSP)₄. The preferred ylide conformation **8** is evidenced by the stereospecific formation of (*Z*)-epoxide through a 4-electron conrotatory ring closure.

In conclusion, we report a first example of chemospecific dioxolane formation from “cross” 1,3-dipolar cycloaddition of methyl phenyldiazoacetate with an electron-rich and an

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(8) Even though 2,4-dinitrobenzaldehyde served as a good dipolarophile, reaction of diazo **1** with 2,4-dinitrobenzaldehyde alone still gave only epoxide product without trace amounts of dioxolane; see the Supporting Information.

electron-deficient aldehyde in the presence of dirhodium acetate catalyst. Carbonyl ylide generated from the carbenoid with the electron-rich aldehyde selectively reacts with the electron-deficient aldehyde to give 2,4,5-triaryl-1,3-dioxolanes in moderate to high yields.

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Supporting Information Available: Experimental procedures and characterization data of all new compounds, as well as X-ray crystallographic data for **4b**, **4l**, and **5l** in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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