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## An Approach Toward Oxidopyrylium Ylides Using Rh(II)-Catalyzed Cyclization Chemistry

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### Abstract

The Rh(II)-catalyzed reaction of the *E*-isomer of 2-diazo-3,6-dioxo-6-phenyl-hex-enoic acid methyl ester was carried out in the presence of various carbonyl compounds and was found to give 1,3-dioxoles in moderate to good yield. In an attempt to prepare the starting -diazo substrate, an unexpected pseudo-dimerization reaction was encountered when 5-phenyl-furan-2,3-dione was heated in the presence of sodium methoxide.

In recent years, a widespread upsurge of activity in the application of carbonyl ylide dipoles to new synthetic transformations has occurred.<sup>1,2</sup> This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for the generation of other types of ylides.<sup>3</sup> A diverse range of chemistry has already surfaced.<sup>1–4</sup> In 1986, work started in the Padwa laboratory to synthesize bridged oxa-substituted bicycloalkanes from the Rh(II)-catalyzed cyclization cascade of -diazo carbonyl compounds.<sup>5a</sup> The domino reaction was shown to proceed by the formation of a rhodium carbenoid intermediate and a subsequent transannular cyclization of the electrophilic carbon onto an adjacent carbonyl group to generate a cyclic carbonyl ylide dipole.<sup>5–7</sup> This was followed by a 1,3-dipolar cycloaddition reaction with an added dipolarophile A=B (Scheme 1).

Our ongoing interest in this procedurally simple methodology led us to focus on the cycloaddition behavior of the related oxidopyrylium dipole **5**, where the extra double bond contained within the ring would not only allow for the formation of the [5+2]-dipolar cycloadduct **6**, but also could produce the isomeric cycloadduct **7**. The [5+2]-cycloaddition of 3-oxidopyrylium ylides is a well precedented reaction and has been used for the rapid access of functionalized seven-membered ring structures.<sup>8</sup> Henderson and Farina originally discovered that [5+2]-cycloadditions can be carried out by heating acetoxy-pyranones such as **8** and a dipolarophile at 130 °C to afford up to 69% of cycloadduct **10**.<sup>9</sup> This reaction was further developed by Sammes, who found that electron rich dipolarophiles were more reactive toward dipole **9** and that the reaction can also be carried out using Et<sub>3</sub>N to generate the oxyppyrylium zwitterion at room temperature.<sup>10</sup> Substituted allenes<sup>11</sup> and dienes<sup>12</sup> have also been successfully engaged as dipolarophiles in intra and intermolecular reactions. The rapid generation of molecular complexity in a relatively easy manner has made this cycloaddition reaction extremely useful for the synthesis of seven-membered ring containing natural

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products. Notably, Wender and coworkers have successfully applied this strategy, in an intramolecular fashion, to the total synthesis of the natural products phorbol and resiniferatoxin.<sup>13</sup> Further examples of intramolecular [5+2]-cycloadditions of pyranones of type **11** for natural product synthesis have also been reported by Heathcock,<sup>14</sup> Ohmori,<sup>15</sup> Magnus<sup>16</sup> and Williams.<sup>17</sup>

Since we were interested in using the Rh(II)-catalyzed reaction of -diazo ketoesters such as **4** as a way to generate various oxidopyrylium ylides, we undertook a study of several methods to synthesize the required precursor -diazo ketoesters. To this end, 5-phenylfuran-2,3-dione (**13**) was prepared in 80% yield by reacting trimethyl (1-phenylvinyl)oxy)silane with oxalyl chloride.<sup>18</sup> Our intention was to heat **13** with methyl acetate in the presence of sodium methoxide with the hope that we'd be able to prepare methyl 3,4,6-trioxo-6-phenylhexanoate acid (**14**), which would then be transformed into the corresponding -diazoketo ester **4**.

However, in our attempts to convert furandione **13** into **14**, we encountered a rather unusual reaction. The major (80%) and unexpected product obtained from the thermal reaction of **14** under basic conditions was identified as 3-benzoyl-4-hydroxy-6-phenyl-2*H*-pyran-2-one (**15**) on the basis of its spectral data<sup>19</sup> and by the procurement of an X-ray crystal structure. The pseudo-dimerization of **13** to **15** can be accounted for by an initial thermal extrusion of carbon monoxide from **13** to give benzoyl ketene **16** as a transient species. Attack of methoxide anion at the electrophilic ketene center in **16** generates the stable anion **17**, which in turn reacts with another molecule of the ketene to furnish the 1,3-dicarbonyl anion **18**. Cyclization of **18** to **19** followed by tautomerization to the more stable enol form nicely accounts for the formation of pyranone **15** (Scheme 5).

In an alternate approach that we next employed for the preparation of -diazo ketoester **4**, we made use of an oxidation reaction of furan **20**.<sup>20</sup> Thus, methyl 2-(furan-2-yl)acetate (**20**) was treated with mCPBA at 0 °C in CH<sub>2</sub>Cl<sub>2</sub> and this resulted in a 6:1-stereomeric mixture of the expected ring-opened butene-diones which were immediately converted to the corresponding -diazo ketoesters (*i.e.*, **4** and **21**) using *p*-nitrobenzenesulfonyl azide and Et<sub>3</sub>N according to the standard Regitz protocol.<sup>21</sup> The two isomeric -diazo compounds were separated by fractional recrystallization. Treatment of the minor *Z*-isomer **4** with a catalytic quantity of rhodium(II) acetate in benzene at 25 °C afforded an unknown dimer (*i.e.* **22**) in 45% yield. Unfortunately, all of our attempts to trap an oxidopyrylium ylide intermediate from the *Z*-isomer **4** using various trapping agents failed to afford any signs of a [5+2]-cycloadduct. The only compound detected in these reactions was dimer **22**.<sup>22</sup>

We also studied the Rh(II)-catalyzed behavior of the major *E*-diazo isomer **21**. This isomeric -diazo ketoester cannot undergo internal cyclization to give a carbonyl ylide dipole and we were curious as to what pathway would be followed with this system. Toward this end, **21** was added to a benzene solution containing DMAD and a catalytic amount of Rh<sub>2</sub>(OAc)<sub>4</sub> under an argon atmosphere at 80 °C. The reaction was monitored by TLC and column chromatographic purification of the crude reaction mixture afforded cycloadduct **23** as the only isolable product in 42% yield. A related cycloadduct (*i.e.*, **24**) was isolated when *N*-methyl maleimide was used as the trapping dipolarophile (Scheme 7). When *N*-methyl succinimide, benzaldehyde, cyclohexanone, or acetone were used as the trapping agents, the analogous cycloadducts **26–29** were obtained in 25–80% yield. Ethyl acetate turned out to be a very efficient trapping agent producing cycloadduct **30** in 80% yield. The overall cycloaddition can be rationalized by an initial reaction of -diazo ketoester **21** with the Rh(II)-catalyst to first generate an electrophilic metallo carbenoid. This species then reacts with the nucleophilic carbonyl oxygen atom of the added dipolarophile to furnish the highly reactive carbonyl ylide intermediate **25**. The presence of the adjacent enone carbonyl group facilitates an intramolecular [1,5]-electrocyclization that leads to the corresponding 1,3-dioxole derivatives **26–30**.<sup>23</sup> A resonance structure of the

carbonyl ylide with the negative charge on the oxygen atom of the enone carbonyl group and a positive charge on the carbonyl C-atom of the added dipolarophile contributes significantly to the resonance hybrid of the transient ylide **25**, thereby favoring the [1,5]-electrocyclization pathway (Scheme 8).

In summary, we have investigated the Rh(II)-catalyzed reaction of the *Z*-isomer of 2-diazo-3,6-dioxo-6-phenyl-hex-4-enoic acid methyl ester and found that a dimer was formed as the major product. We have also shown that the Rh(II)-catalyzed reaction of the related *E*-isomer in the presence of various carbonyl compounds undergoes cyclization to give substituted 1,3-dioxoles as the major products. An unexpected pseudo-dimerization process was also encountered when the thermolysis of 5-phenyl-2,3-dione was carried out in the presence of sodium methoxide.

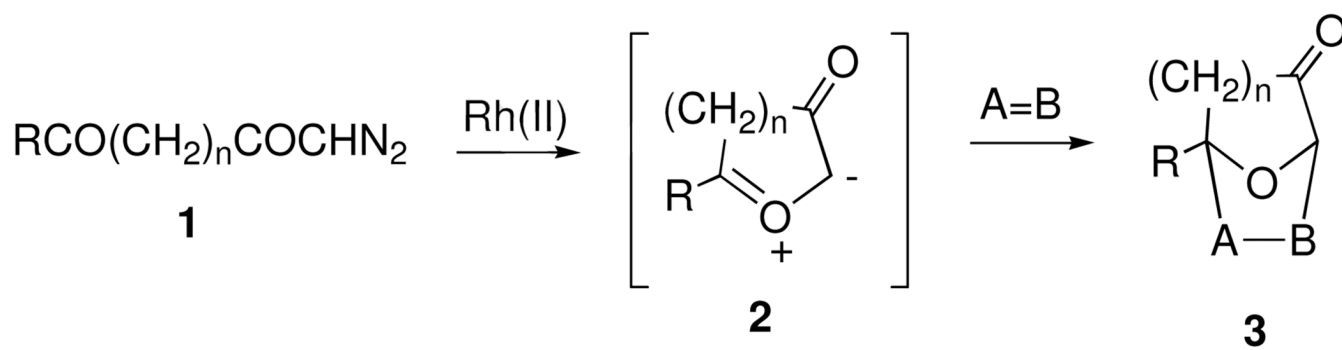
## Acknowledgments

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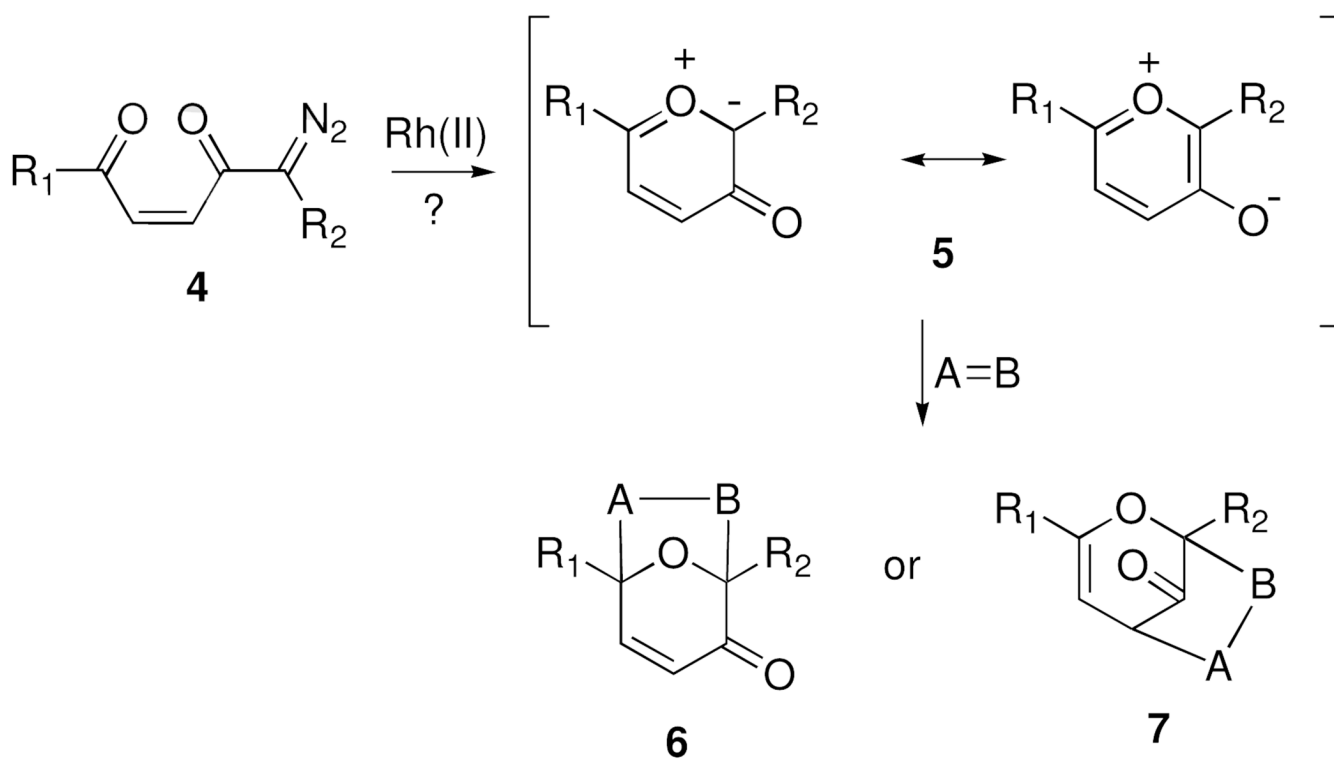
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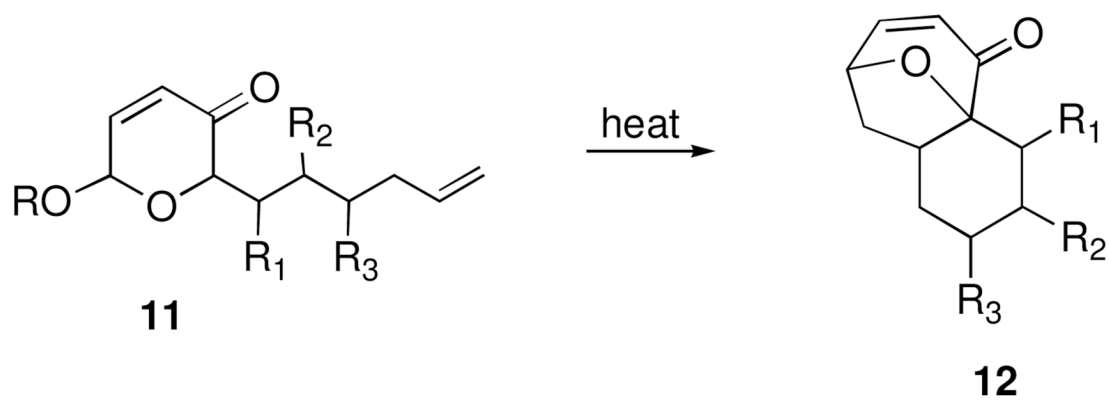
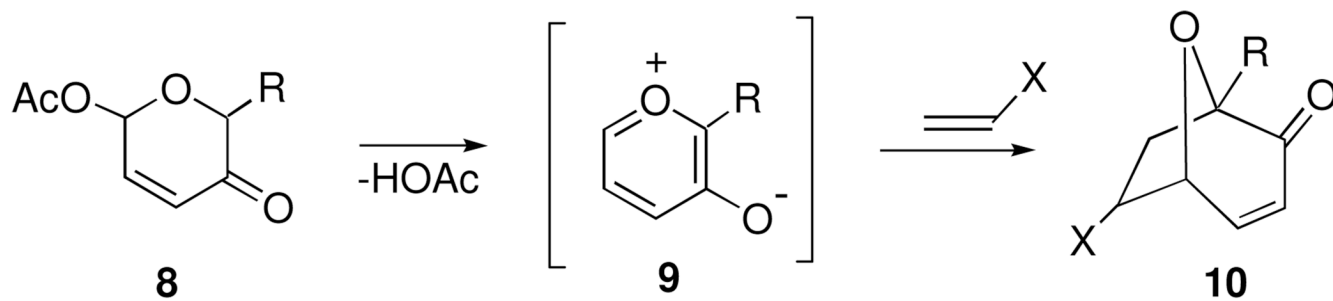
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22. The reaction of **4** with a number of Rh(II) catalysts in several solvents and at different concentrations using diverse trapping agents only led to varying quantities of dimer **22** together with a tarry residue which resisted purification. Our attempts to obtain an X-ray crystal structure of dimer **22** also failed due to the amorphous nature of the solid.
23. For some examples of 1,3-dioxole formation during the decomposition of diazocarbonyl compounds in the presence of simple aldehydes and ketones, see: (a) Weigand F, Dworschak H, Koch K, Konstas S. *Angew. Chem* 1961;73:409. (b) Alonso ME, Jano P. *J. Heterocycl. Chem* 1980;17:721. (c) Huisgen R, De March P. *J. Am. Chem. Soc* 1982;104:4952. (d) Huisgen R, Fisera L, Giera H, Sustmann R. *J. Am. Chem. Soc* 1995;117:9671. (e) Russell AE, Brekan J, Gronenberg L, Doyle MP. *J. Org. Chem* 2004;69:5269. [PubMed: 15287769] (f) Doyle MP, Hu W, Timmons DJ. *Org. Lett* 2001;3:933. [PubMed: 11263919]



Scheme 1.

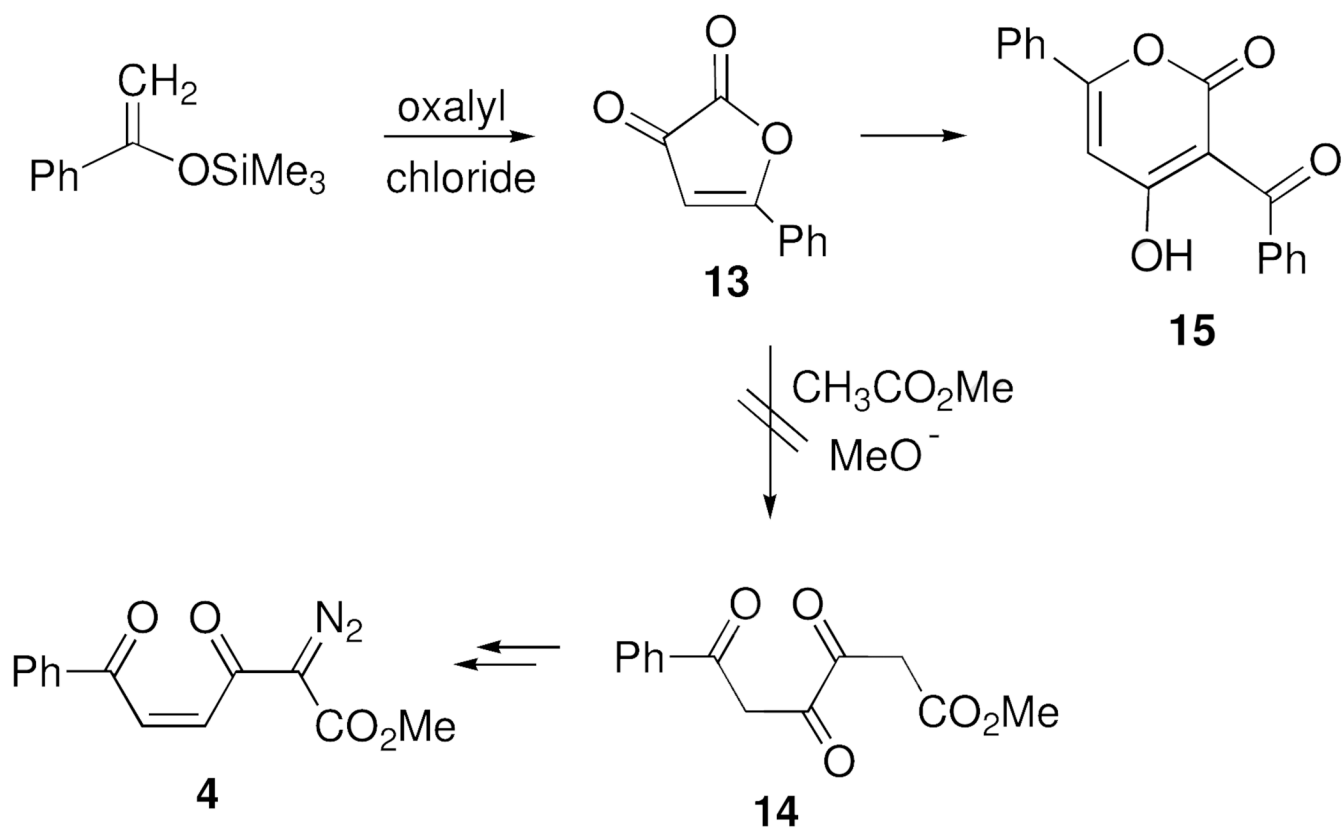


Scheme 2.

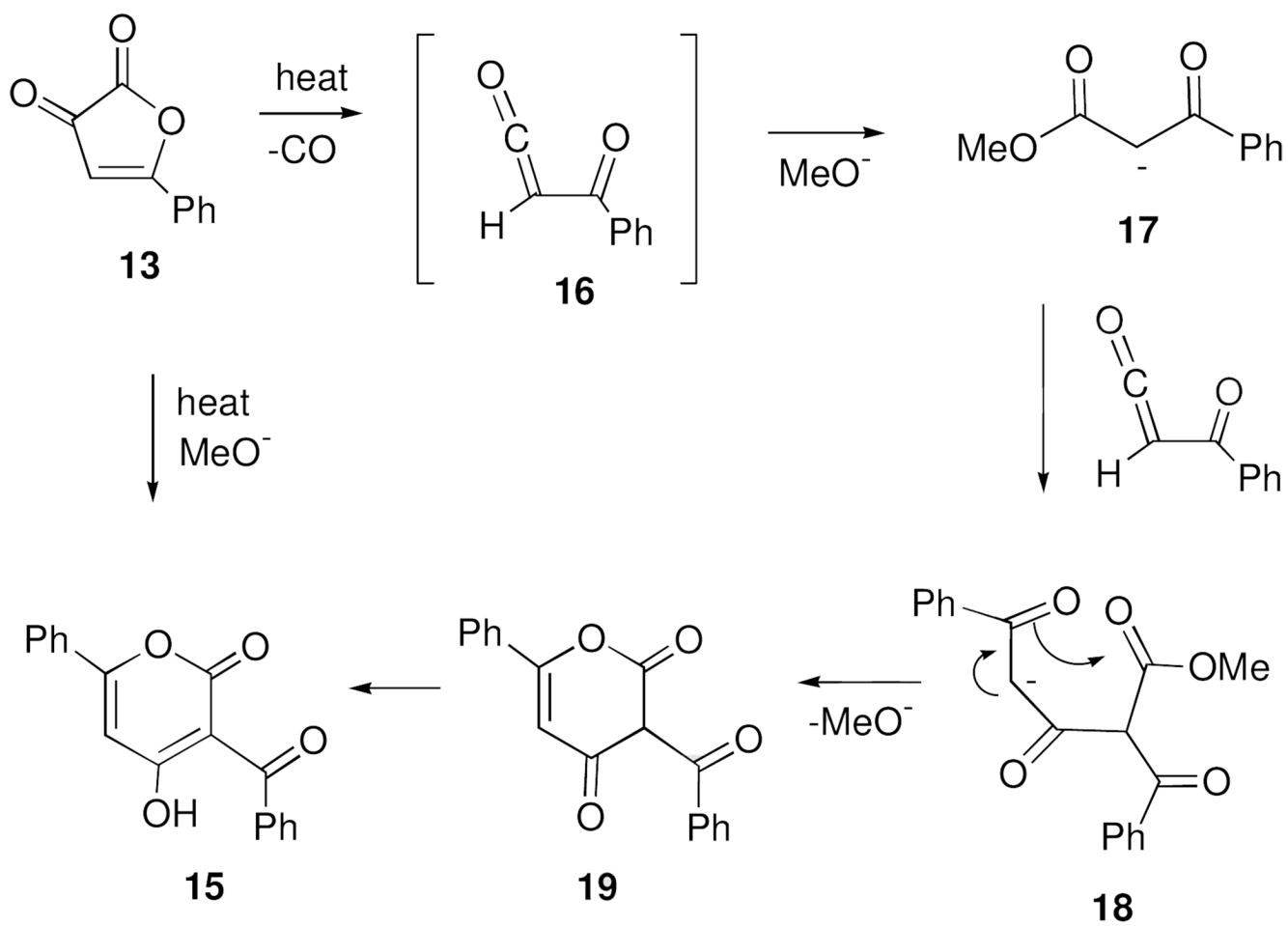


Scheme 3.

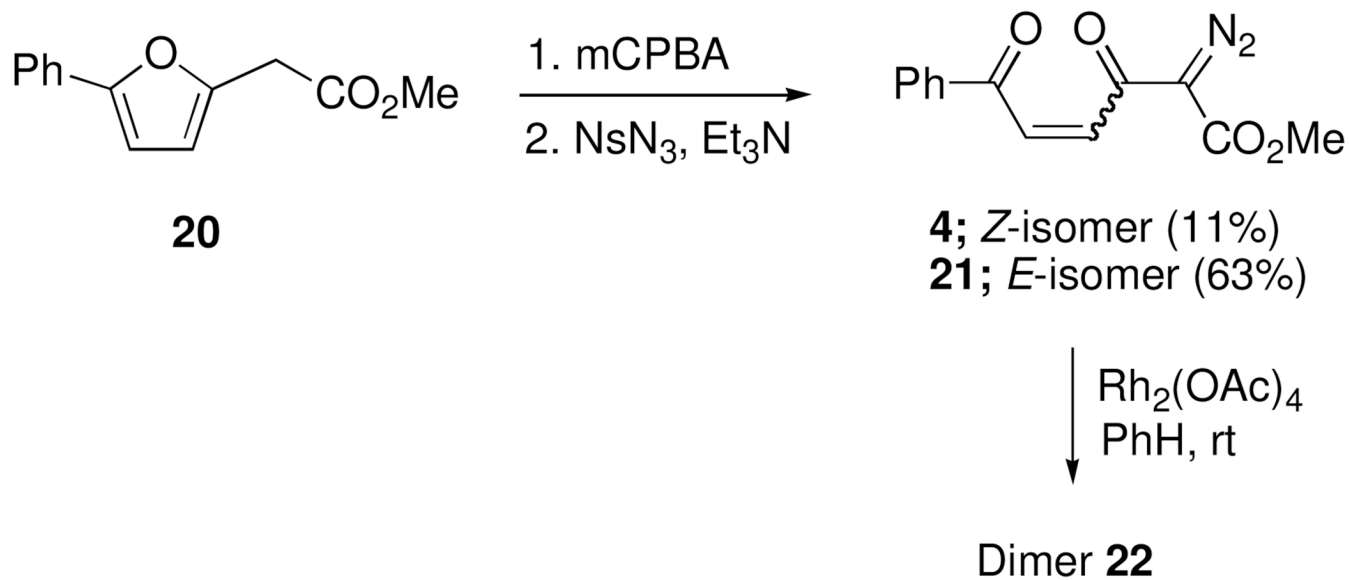




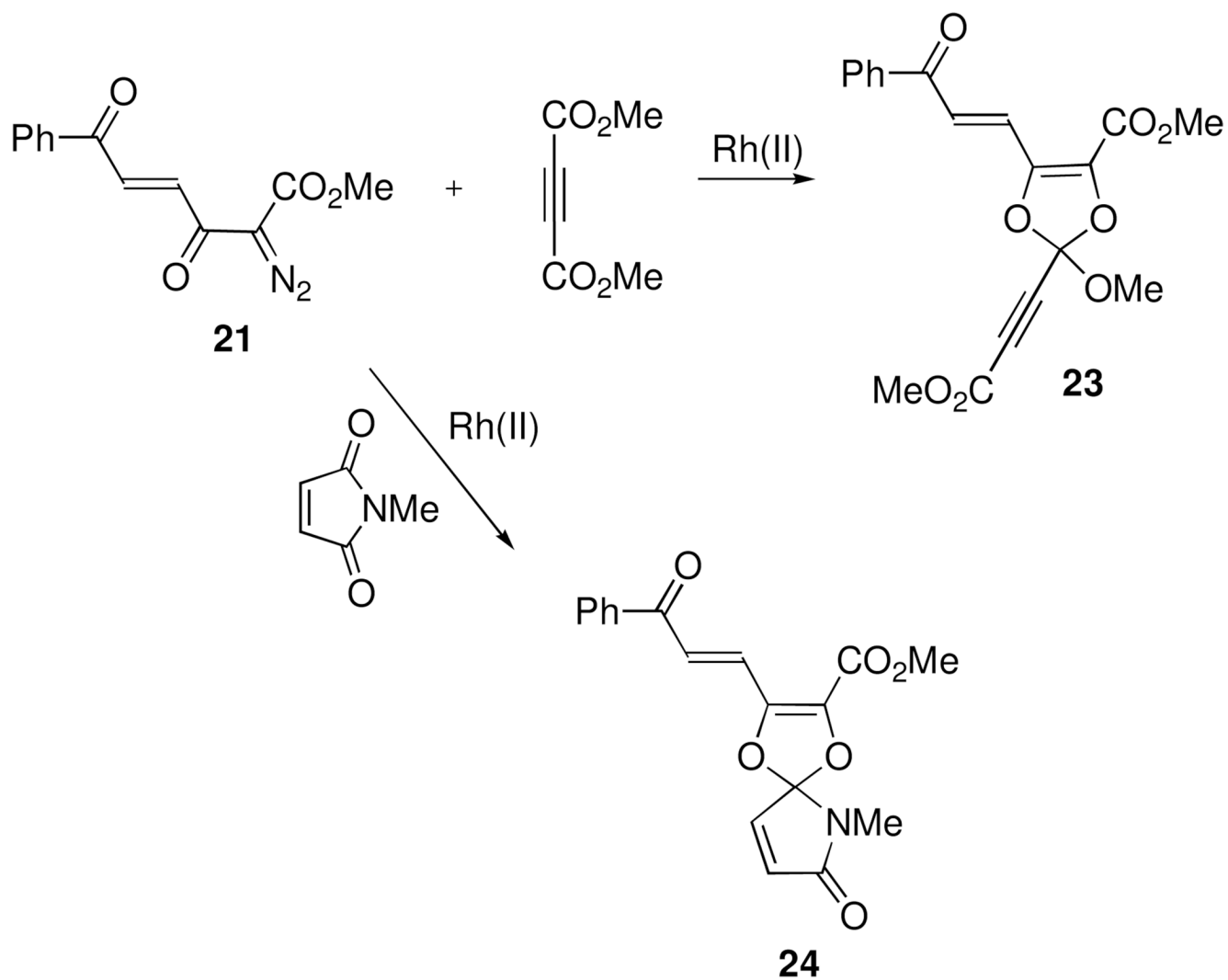
Scheme 4.



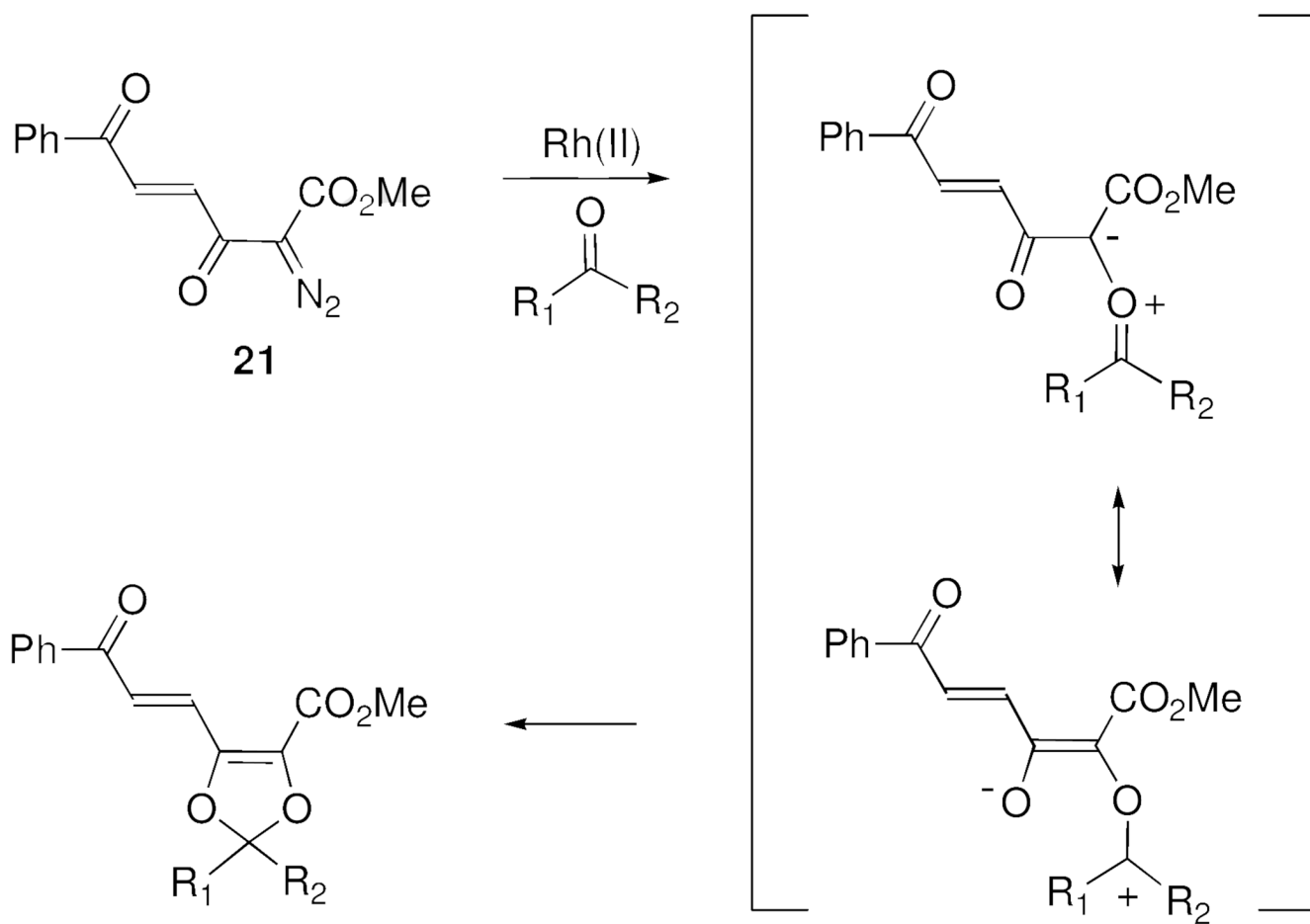
Scheme 5.



Scheme 6.



Scheme 7.



**26**;  $R_1 = CH_2CH_2$ ;  $R_2 = N(CH_3)CO$  (25%)

**27**;  $R_1 = Ph$ ;  $R_2 = H$  (25%)

**28**;  $R_1 = R_2 = (CH_2CH_2)$  (45%)

**29**;  $R_1 = R_2 = CH_3$  (80%)

**30**;  $R_1 = OC_2H_5$ ;  $R_2 = CH_3$  (80%)

Scheme 8.