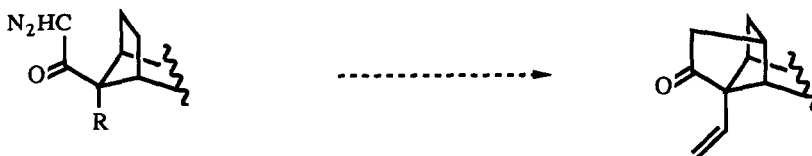


## REGIOCONTROL BY ELECTRON WITHDRAWING GROUPS IN THE Rh-CATALYZED C-H INSERTION OF $\alpha$ -DIAZOKETONES

Gilbert Stork and Kazuhiko Nakatani†  
Department of Chemistry, Columbia University,  
New York, N.Y. 10027

**Summary:** It is possible to control the regiochemistry of the Rh-catalyzed insertion of  $\alpha$ -diazoketones into C-H bonds by taking advantage of the greatly reduced rate of insertion into methylenes which are  $\alpha$  or  $\beta$  to a carboxyl function. The 2-carboxyethyl group is especially useful for this purpose because it can be transformed eventually into a variety of other substituents.

In the course of an approach to the synthesis of gelsemine we required the transformation shown in Scheme 1. This required finding a group R which would 1) survive the Rh-catalyzed C-H insertion reaction of a diazoketone; and 2) be easily transformable into a vinyl substituent. Simple possibilities such as, *inter alia*, a vinyl group ( $R = \text{CH}=\text{CH}_2^1$ ) or oxygen-containing groups (e.g.  $R = \text{CO}_2\text{R}^2$  or  $\text{CH}_2\text{OR}^3$ ), are unsuitable because they undergo metal-catalyzed reactions with diazoketones.

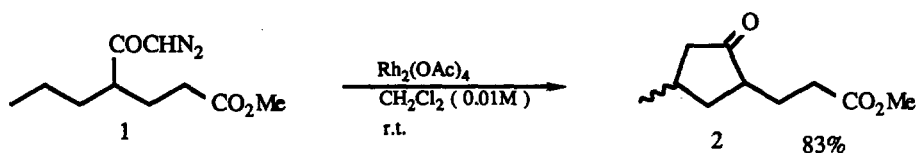


Scheme 1

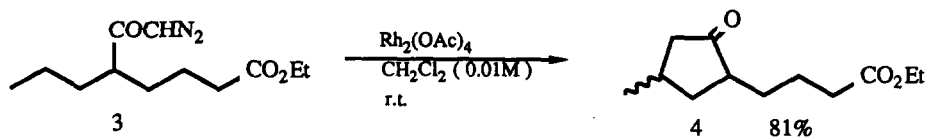
In the course of their extensive studies on Rh(II)-catalyzed C-H insertion reactions,<sup>4</sup> Taber and Ruckle reported that electron withdrawing substituents, such as vinyl and phenyl groups, decrease the reactivity of the adjacent C-H bond to such insertions.<sup>4a</sup> In the reaction of  $\alpha$ -diazo- $\beta$ -keto esters catalyzed by  $\text{Rh}_2(\text{OAc})_4$ , an aliphatic methylene was preferred over an allylic or a benzylic methylene by factors of 2.3 and 2.9, respectively.<sup>5</sup> This suggested the possibility that more electron

withdrawing groups, such as ketones or esters, might protect not only their  $\alpha$ , but their  $\beta$  C-H bonds as well, against the insertion reaction. Should this hypothesis prove correct, the resulting selectivity should be generally useful since a propionate substituent ( $R=CH_2CH_2CO_2Me$ ) can be transformed not only into a vinyl group (e.g. by oxidative decarboxylation of the corresponding acid with lead tetraacetate and cupric acetate<sup>6</sup>), but also into a variety of other substituents.

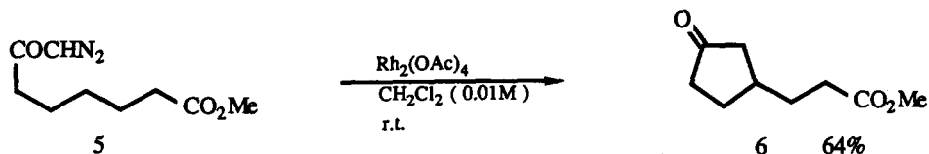
We now show that an ester group indeed steers diazo ketone insertion away from its  $\alpha$  as well as from its  $\beta$  methylenes. Cyclization of **1** clearly shows the protection of the  $\alpha$ -methylene to the ester: to a 0.01M solution of **1**<sup>7</sup> (133mg) in 63ml of  $CH_2Cl_2$ ,  $Rh_2(OAc)_4$  (14mg, 5mol%) was added at room temperature. After gas evolution ceased (ca. 5min.) the solvent was removed *in vacuo*. The residue was diluted with ether and washed with water. The organic phase was dried over  $MgSO_4$  and concentrated *in vacuo*. The <sup>1</sup>H-NMR spectrum of the crude products (106mg) showed no triplet methyl signals, but there were now two doublet signals, one at 1.09ppm ( $J=6.5Hz$ ) and the other at 1.14ppm ( $J=6.5Hz$ ). After purification by flash chromatography, the cyclopentanone ester **2**<sup>8</sup> (96mg, 83% yield) was obtained as a mixture of two stereoisomers.



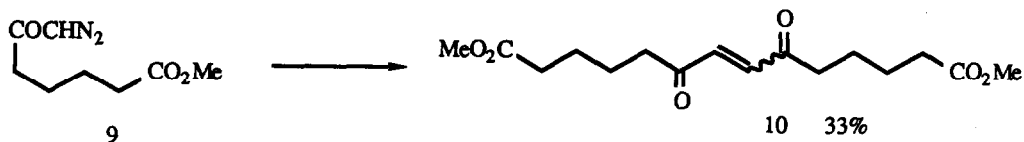
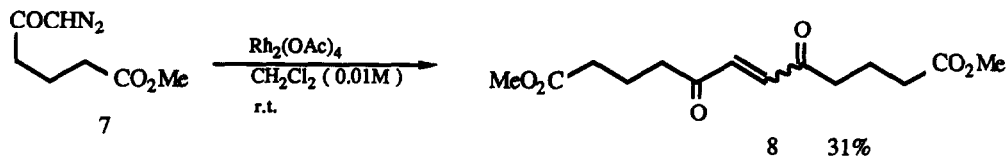
Result of the competition between the two possible cyclopentanones from the cyclization of **3**<sup>9</sup> shows that the protection by the ester function extends to the  $\beta$ -methylene group: The Rh(II)-catalyzed reaction of diazoketone **3** led, after flash chromatography, to an 81% yield of cyclopentanone **4**, as a mixture of two stereoisomers.<sup>8</sup>



As might be expected, protection against insertion is no longer effective once the  $\gamma$ -carbon to the ester is reached. Reaction of 5 proceeds "normally" to give cyclopentanone 6 in 64% yield by insertion into the  $\gamma$ -CH<sub>2</sub> to the ester.



Finally, one might wonder what would result if the only possible insertion were into the  $\alpha$  or the  $\beta$ -methylenes to an ester function. In such situations, the reactions give rise to complex mixtures and low recovery. Cyclopentanone formation was, at best, a minor pathway and the major isolated products (~30%) were the result of "dimerization" as in 7 to 8 and 9 to 10.<sup>10,11</sup>



We believe that the ability of a carboxyl and, presumably, other strongly electron withdrawing groups to protect C-H bonds against diazoketone insertion should prove a useful feature in extending the range of these important reactions.

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**References and Notes.**

† Research Associate

- 1) For a general review of intramolecular cyclopropanation, see S.D.Burke and P.A.Grieco, *Organic Reactions*, **26**, 361 (1979). For references of vinylogous Wolff rearrangement of  $\beta,\gamma$ -unsaturated diazoketones, see A.B.Smith,III, B.H.Toder and S.J.Branca, *J. Am. Chem. Soc.*, **106**, 3995 (1984).
- 2) A.Gillon, D.Ovadia, M.Kapon and S.Bien, *Tetrahedron*, **38**, 1477 (1982).
- 3) a) M.C.Pirung and J.A.Werner, *J. Am. Chem. Soc.*, **108**, 6060 (1986).  
b) E.J.Roskamp and C.R.Johnson, *ibid.*, **108**, 6062 (1986).
- 4) a) D.F.Taber and R.E.Ruckle,Jr., *J. Am. Chem. Soc.*, **108**, 7686 (1986).  
b) K.Nakatani, *Tetrahedron Lett.*, **28**, 165 (1987) and references cited therein.
- 5) Regioselectivity may also vary depending on the specific type of diazoketone: cf relative insertion rates into aromatic vs. aliphatic C-H of  $\alpha$ -diazo- $\beta$ -keto-esters and  $\alpha$ -diazoketones. Compare ref. 4a and ref. 4b.
- 6) R.A.Sheldon and J.K.Kochi, *Organic Reactions*, **19**, 279 (1972).
- 7) Prepared from the dibenzyl ester of propylmalonic acid in 4 steps (cat. NaOMe, methyl acrylate / H<sub>2</sub>, 5% Pd-C, EtOAc / xylene reflux / (COCl)<sub>2</sub>, PhH / CH<sub>2</sub>N<sub>2</sub>).
- 8) Products were identified by <sup>1</sup>H-NMR, IR and mass spectral data.
- 9) Prepared from the dibenzyl ester of propylmalonic acid in 4 steps; NaH, BrCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Et / H<sub>2</sub>, 5% Pd-C, EtOAc / xylene reflux / (COCl)<sub>2</sub>, PhH / CH<sub>2</sub>N<sub>2</sub>.
- 10) Each insertion reaction mentioned in this paper was carried out at least twice.
- 11) In the case of 9, a small amount (~9%) of the insertion product, the methylester of 3-oxocyclopentylacetic acid was isolated.

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