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Stereoselective Synthesis of Disubstituted 3(2H)-Furanones *via* Catalytic Intramolecular C-H Insertion Reactions of α-Diazo-β-Keto Esters Including Asymmetric Induction

Tao Ye and M. Anthony McKervey*

School of Chemistry, The Queen's University, Belfast BT9 5AG, U.K.

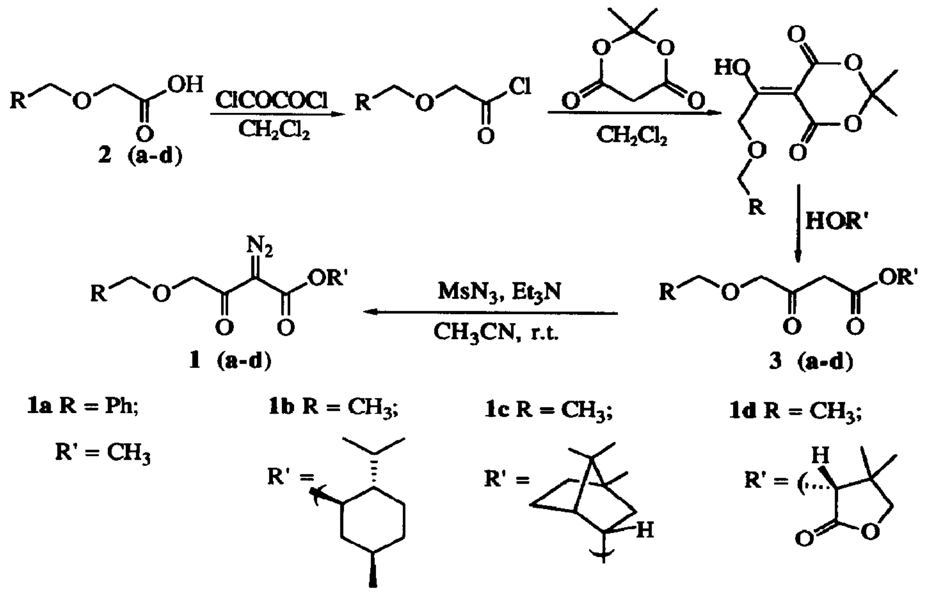
Bridget D. Brandes and Michael P. Doyle

Department of Chemistry, Trinity University, San Antonio, Texas 78212, U.S.A.

***Abstract:** Rhodium(II) catalysed decomposition of γ-alkoxy-α-diazo-β-ketoesters produce cis-2,5-disubstituted -3(2H)-furanones with high (>97%) stereoselectivity. The combination of a chiral auxiliary in the ester moiety of the diazo precursor and a chiral catalyst can lead to asymmetric synthesis with diastereoselectivities up to 61% de.*

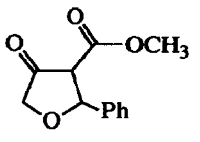
O-Heterocyclic ring systems are prominent features of numerous naturally occurring compounds and the development of simple, but effective methods for their stereocontrolled synthesis is a goal of considerable practical importance. The past twenty years have witnessed a significant increase in the utilization of diazocarbonyl compounds as precursors in carbon-carbon bond forming reactions. Intramolecular carbenoid insertion into C-H bonds has assumed strategic importance in organic synthesis.[1] Transition metal compounds are effective catalysts for carbenoid formation from diazocarbonyl compounds.[1b,2] Recently dirhodium(II) compounds have been recognized as superior in versatility, generality and selectivity to other routinely employed transition metal catalysts for C-H insertion.[1b,c,3] Adams and coworkers[4] have reported the construction of disubstituted 2,5-3(2H)-furanones *via* an intramolecular C-H insertion reaction of α-alkoxy diazoketones, the disubstitution adjacent to the ether oxygen of the 3(2H)-furanone showing a pronounced selectivity in favour of *cis*-isomers. Doyle and coworkers have reported *cis* selectivity in the formation of β-lactams *via* carbenoid C-H insertion α to a carboxylate ester of a diazoacetoacetamide.[5a] Furthermore, chiral dirhodium(II) catalysts have been designed to achieve enantiocontrol in the C-H insertion process and notably high levels of enantioselection have been observed in γ-lactone[3d] and substituted chromanone[3b] formation. However, in general, diastereocontrol in these carbenoid reactions is not yet predictable.[5b] As part of a programme of investigation of rhodium-catalysed carbenoid reactions, we report herein the stereoselective construction of *cis* disubstituted 4,5-3(2H)-furanone esters *via* catalytic decomposition of α-diazo-β-ketoesters with asymmetric induction.

γ-Alkoxy-α-diazo-β-ketoesters of type **1** were prepared as outlined in **Scheme 1**. γ-Alkoxy-carboxylic acid **2** was first converted into the corresponding acid chloride which was treated with Meldrum's acid followed by subsequent esterification with the appropriate alcohol to form γ-alkoxy-β-ketoesters **3**.[6] Diazo transfer with mesyl azide completed the preparation of the γ-alkoxy-α-diazo-β-ketoesters **1**[7] (overall yields, 47% **1a**; 36% **1b**; 60% **1c**; 67% **1d**)

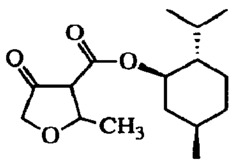


Scheme 1

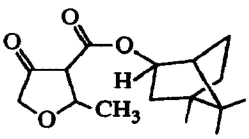
Cyclisation of **1b**, **1c** and **1d** with rhodium(II) carboxylates **6-11** (0.5mol %) in dichloromethane at 0 °C under N_2 afforded in good yield, after purification by chromatography on silica gel, the C-H insertion products **4b-d** as *cis* isomers only (**Table 1**).[8] When **1a** was treated with catalyst at 0 °C, the resulting product contained only a low percentage of **4a** (**Table 1**).[8] However, when this cyclisation was repeated in refluxing dichloromethane, pure **4a** was obtained stereospecifically as the *cis* isomer in 63% yield. The precursor **1a** may be less reactive than **1b-d** because of greater steric demands at the C-H insertion site. Therefore, to obtain a higher yield of **4a** from the cyclisation of **1a** required a higher reaction temperature. The *cis* stereochemistry of each product, estimated to be > 97% by ^1H NMR analysis, was verified by isomerization to the *trans* stereoisomers **5a-d** *via* treatment with potassium *tert*-butoxide in dry tetrahydrofuran. Further support for the assignment of the relative stereochemistry was provided by the observation that, in the ^{13}C NMR spectra,[9] the carbon atom of the ester carbonyl in **4a-d** is always shifted upfield relative to the carbon in the isomerization products **5a-d**. Such shielding in the ^{13}C spectra would be a consequence of steric compression.



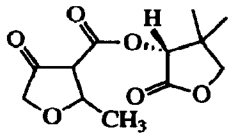
4a(*cis*)
5a(*trans*)



4b(*cis*)
5b(*trans*)



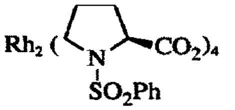
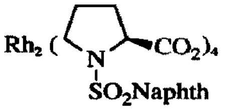
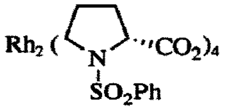
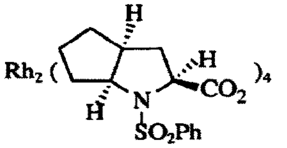
4c(*cis*)
5c(*trans*)



4d(*cis*)
5d(*trans*)

A certain degree of asymmetric induction was obtained in the cyclisation of **1a-d** when chiral rhodium(II) carboxylates **7-11** were employed.[10] The results are summarised in **table 1**.[11]

Table 1 Cyclisation of γ-alkoxy-α-diazo-β-ketoesters **1a-d** with rhodium(II) carboxylates **6-11** in CH_2Cl_2

3(2H)-Furanones / Catalyst	**4a**		**4b**		**4c**		**4d**	
	yield %	ee %	yield %	de %	yield %	de %	yield %	de %
Rh(II) acetate **6**	59	0	40	18	52	2	59	7
Rh(II) mandelate **7**	62	14	72	6	72	3	51	28
 **8**	63	9	64	61	67	16	64	6
 **9**	58	5	59	35	39	14	69	5
 **10**	64	8	67	47	66	14	67	7
 **11**					68	4	74	10

As seen from **table 1**, the phenyl substituted furanone **4a** derived from the decomposition of the corresponding achiral diazoester **1a** through the use of various chiral Rh(II) catalysts **7-10** displayed low levels of asymmetric induction. However, when chiral γ-alkoxy-α-diazo-β-ketoester **1b**, which contains the menthyl group as a chiral auxiliary, was combined with rhodium(II) benzenesulphoneprolinate **8**, considerable diastereoselectivity enhancement was achieved, the % de value being more than 60%. Achiral rhodium (II) acetate decomposition of **1b**, on the other hand, gave considerably lower diastereoselection. Although (R)-pantolactone has been used as a chiral auxiliary in rhodium(II) catalyzed cyclopropanations with vinyldiazomethanes with high diastereoselectivity,[12] the effect of this chiral auxiliary in the construction of furanone **4d** from precursor **1d** is to give only lower diastereoselectivity than does the corresponding menthyl derivative. Another α-diazocarbonyl precursor **1c**, with [(1S)-*endo*]-(-)-borneol as a chiral auxiliary undergoes furanone formation which exhibits a lower diastereoselection. It seems that a sterically elongated chiral attachment is more suitable for achieving high % de values than are "tighter" attachments.

In conclusion, this is the first reported study of the stereoselective cyclization of γ-alkoxy-α-diazo-β-ketoesters to substituted furanones using chiral catalysts. The exclusive *cis* selectivity in product formation combined with the diastereomeric excess of up to 61% in the synthesis of **4b** is encouraging.

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6 Oikawa, Y.; Sugano, K. and Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.

7 Taber, D. F.; Ruckle, R. E., Jr. and Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.

8 All four products exhibited satisfactory spectroscopic properties and gave satisfactory microanalytical data on combustion.

9 δ_C values for the ester carbonyl were: 163.00, 163.06, 163.12, 163.36, 168.25, 167.42, 168.22 and 166.36 ppm corresponding to **4a**, **4b**, **4c**, **4d**, **5a**, **5b**, **5c** and **5d**, respectively.

10 The rhodium(II) catalysts were prepared from the sodium salt of rhodium (II) carbonate and the appropriate carboxylic acid by displacement reaction. See: Pruchnik, F.; James, B. R. and Kvintovics, P. *Can. J. Chem.* **1986**, *64*, 936.

11 The ee was established by NMR chiral studies employing $Eu(hfc)_3$. The de were determined by HPLC.

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