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Site Selectivity in the Rhodium(II)-Catalyzed Reaction of α-Diazoimides. Ligand and Substituent Effects

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Abstract: The product distribution obtained from Rh(II)-catalyzed decomposition of α-diazoimides derived from glycine methyl ester has been found to be selectively controlled by the proper choice of catalyst. When the reaction was carried out using perfluorinated ligands, the diazoimide cyclized to produce an isomünchnone dipole whose formation could be monitored by NMR spectroscopy. Reaction of the dipole with a trapping agent such as *N*-phenylmaleimide resulted in the isolation of a 1,3-dipolar cycloadduct in high yield. The product distribution changed dramatically when rhodium(II)-acetate was employed as the catalyst. The products obtained from this reaction were derived from an azabicyclic epoxide intermediate. The catalyst effect can be modulated by the addition of $Sc(OTf)_3$ as a Lewis acid or by using nitromethane as the solvent. Changing the nature of the interacting carbonyl group had little effect on the cyclization pathways.

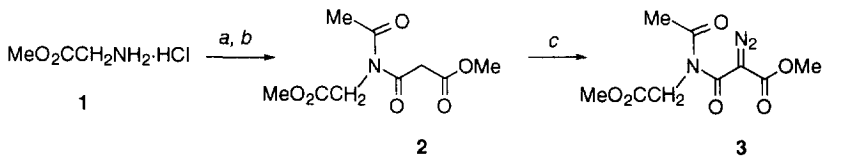
1,3-Dipolar cycloaddition chemistry is an especially versatile process for the preparation of many different types of five-membered heterocyclic rings.[1-4] The continuing popularity of this method rests, in part, on the ability to generate several contiguous stereogenic centers in one synthetic operation.[5-12] Regiochemistry is generally controlled by the nature of the groups attached to the dipole and/or dipolarophile.[13-18] π-Facial selectivity, which arises when either of the addends possesses diastereotopic faces, is also an important stereochemical issue.[19-21] Several factors such as steric hindrance, complexation of the interacting 4π and 2π-components, secondary orbital factors, and electrostatic interactions are known to influence facial selectivity in these [4+2]-cycloadditions.[22]

As a consequence of our long-standing interest in carbonyl ylide dipolar cycloadditions using diazo precursors,[23] we have been investigating the Rh(II)-catalyzed reaction of α-diazo carbonyl compounds derived from α-amino acid esters.[24] Metallo carbenoids obtained from diazo compounds by transition metal-catalyzed decomposition reactions have attracted considerable attention in recent years as valuable intermediates for the efficient construction of structurally complex substrates from readily accessible precursors.[25] Rhodium(II) carboxylates and carboxamides have emerged as the catalysts of choice for chemo- and stereoselective diazo carbonyl reactions.[26] The resulting rhodium carbenoids can undergo a variety of synthetically valuable reactions including cyclopropanation,[27] X-H insertion (X = C, O, N)[28] or ylide formation by intramolecular ring-closure onto adjacent carbonyl groups.[29] For diazo compounds possessing several functional groups, the efficient and predictable control of chemoselectivity constitutes an important prerequisite for synthetic applications.[30] Previous work in this area by several research groups clearly revealed the crucial role of molecular structure and nature of the catalyst for discriminating amongst the different reaction pathways.[31] In a preliminary

communication,[24] we reported that the product distribution encountered in the Rh(II)-catalyzed reaction of certain α-diazoimides could be selectively controlled by the nature of the ligand groups on the catalyst. In the present paper, we describe additional studies dealing with the influence of catalyst, solvent, substituent groups and additives on the chemoselectivity and stereochemical outcome of these reactions.

Results and Discussion

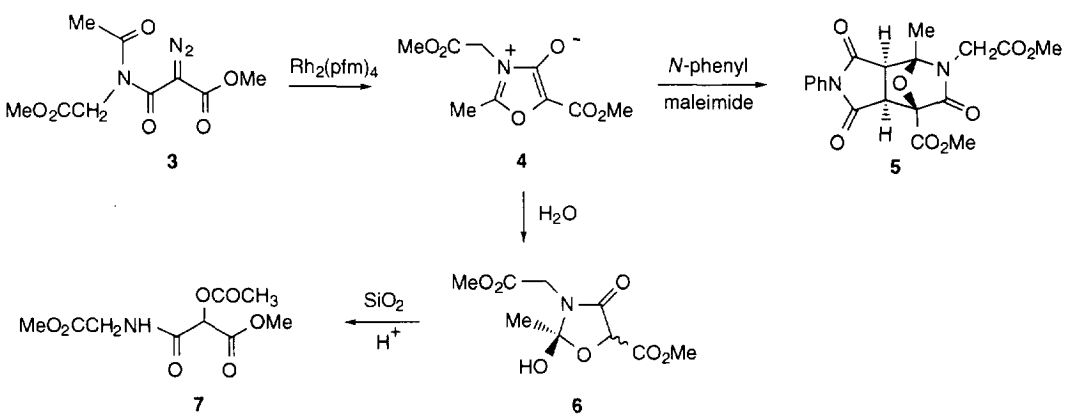
The achiral model substrate **3** was prepared in three steps and good overall yield (63%) from glycine methyl ester hydrochloride (**1**). Thus, treatment of **1** with acetyl chloride in the presence of triethylamine and subsequent condensation with methyl malonyl chloride gave imide **2**, which was transformed into the desired diazoimide **3** by standard diazo transfer methodology.[32] In this reaction sequence, aqueous workup at any stage led to considerable loss of material due to the water solubility of the products.



(a) AcCl, NEt_3; (b) $ClCOCH_2CO_2Me$, C_6H_6, Δ; (c) $CH_3SO_2N_3$, NEt_3 (69% overall)

In the presence of rhodium(II) perfluorobutyroamidate [$Rh_2(pfm)_4$] and using *N*-phenylmaleimide as the dipolarophile in benzene, the *exo*-cycloadduct **5** was formed in 95% yield *via* five-ring cyclization of the initially formed rhodium carbenoid onto the acetyl oxygen atom followed by a subsequent [3+2]-cycloaddition of the intermediate isomünchnone **4** (Scheme I).[33] A small amount (≤3%) of the *endo*-isomer was also observed. When the reaction was carried out in $CDCl_3$ without any added dipolarophile, the smooth transformation of diazoimide **3** into the mesoionic dipole **4** could be monitored directly by ^{1}H-NMR. Although intermediate

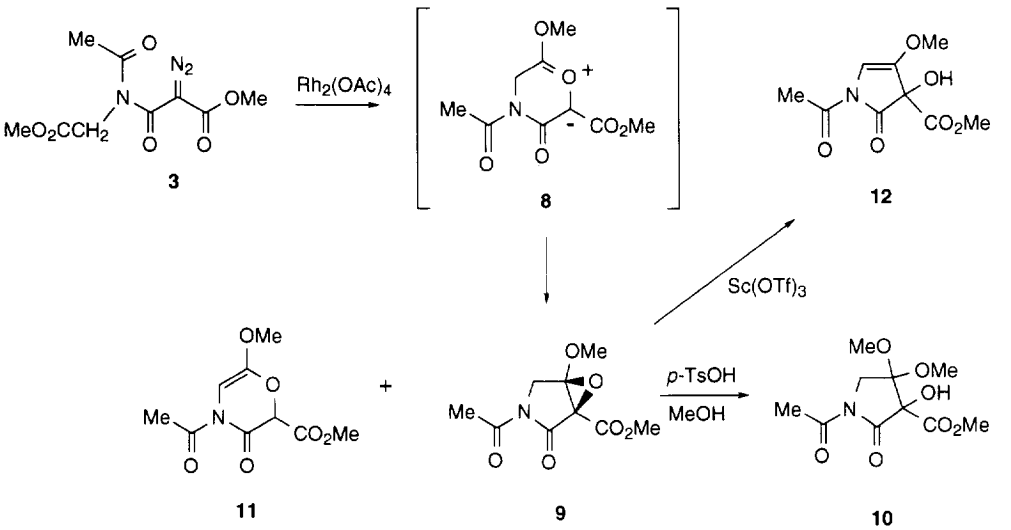
Scheme I



4 was too labile for isolation, it was readily trapped with *N*-phenylmaleimide to give cycloadduct **5**. Upon addition of water to the isomünchnone dipole, an equilibrium mixture of the diastereomers of hemiketal **6** formed, which rearranged to acetate **7** during column chromatography (84% from **3**). Products derived from C-H insertion at the methylene group or six-ring cyclization onto the ester carbonyl were not observed.

We next decided to test whether the observed preference for isomünchnone formation through five-ring cyclization could be altered as a function of the ligand on the rhodium catalyst. While the fluorinated analogs (*i.e.*, rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$], rhodium(II) trifluoroacetate [$Rh_2(tfa)_4$], and [$Rh_2(pfm)_4$]) all showed the same reactivity pattern, the product distribution changed dramatically when rhodium(II) acetate [$Rh_2(OAc)_4$] was employed as the catalyst. In this case, only a small quantity of the isomünchnone cycloadduct **5** was observed when the reaction was performed in refluxing benzene in the presence of *N*-phenylmaleimide. The major product was epoxide **9**, produced by attack of the rhodium carbenoid on the ester carbonyl

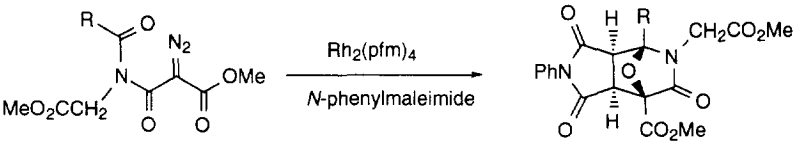
Scheme II



group (Scheme II). The epoxide proved to be too labile to isolate by column chromatography, however its structure was established by its characteristic ^{13}C-NMR signals (δ = 63.5 and 88.8 ppm) and *in situ* trapping with methanol to produce hydroxy ketal **10**. This compound could be isolated in 84% yield from **3** and was fully characterized. In addition, *ca* 3% of enol ether **11** was also found in the crude reaction mixture. A similar product distribution was encountered when the reaction was carried out in the presence of dimethyl acetylenedicarboxylate (DMAD), or without any added dipolarophile. While the enol ether **11** seems to stem from a proton shift in the six-membered carbonyl ylide intermediate **8**,[34,35] it is not clear whether epoxide **9** is derived from charge collapse of the same intermediate or whether its formation is *via* a direct cyclopropanation of the ester C=O group by the rhodium carbenoid.[36]

The above studies demonstrate that the reactivity of the transient rhodium carbenoid derived from α-diazoimide **3** is markedly dependent on the electronic nature of the rhodium catalyst, with a distinct preference for isomünchnone formation with the fluorinated ligands. When rhodium(II) caprolactamate [$Rh_2(cap)_4$] is used as the catalyst, roughly equal amounts of cycloadduct **5** and epoxide **9** are observed. There are a growing number of examples in the literature which address the question of chemoselectivity of diazocarbonyl compounds that contain two different reaction sites.[31,37] These studies show that the chemoselectivity of the reaction is greatly affected by the nature of the bridging ligand attached to the metal. In a recent study, Pirrung and Morehead suggested that a very important parameter that controls catalyst selectivity is ligand polarizability,[38] implying a significant degree of backbonding between the metal complex and the carbenoid. Several conclusions can be drawn from the ligand studies with diazoimide **3**. While our results show that C-H insertion does not compete with ylide formation, either of the two available carbonyl groups can successfully capture the intermediate rhodium carbenoid. Moreover, it is clearly the electronic nature and not the steric size of the ligand groups (*e.g.*, acetate *vs* trifluoroacetate) that determines the site selectivity in the cyclization step. Our initial assumption was that the carbenoid species generated from the perfluorinated rhodium catalysts is a highly electrophilic species,[30] and consequently, the observed change in chemoselectivity is reflective of the relative order of nucleophilicity of the two competing carbonyl groups. We, therefore decided to systematically alter the substitution pattern of the interacting amido group in order to gain a better understanding of the factors responsible for the observed ligand effects.

This led us to study the Rh(II)-catalyzed reaction of diazoimides **13-16** that were prepared by acylation of glycine methyl ester **1** with the appropriate acid chloride, followed by malonation and subsequent diazo transfer. Reaction of the diazoimides with *N*-phenylmaleimide and $Rh_2(pfm)_4$ in refluxing benzene afforded isomünchnone cycloadducts **17-20** in high yield (*ca.* 85%). In no case was an epoxide detected. When

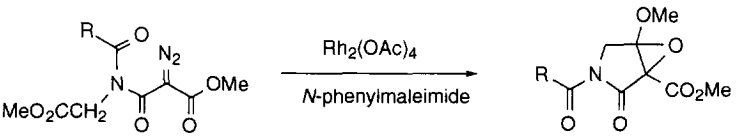


13; R=C_6H_5
14; R=*p*-MeO(C_6H_4)
15; R=*p*-NO_2(C_6H_4)
16; R=OMe

17; R=C_6H_5
18; R=*p*-MeO(C_6H_4)
19; R=*p*-NO_2(C_6H_4)
20; R=OMe

$Rh_2(OAc)_4$ was used as the catalyst, none of the isomünchnone cycloadducts were obtained. Instead, epoxides **21-23** were formed in 80-90% yield. The epoxides could not be purified, as they underwent extensive decomposition upon silica gel chromatography. However, their structures could be assigned on the basis of their characteristic spectral properties, which resemble those of epoxide **9** (see Experimental Section).

The above results establish that all three aroyl substituted diazoimides (*i.e.*, **13-15**) behave in a manner similar to the acetyl diazoimide system **3**. With the perfluorinated ligands, isomünchnone formation is the preferred pathway even with the *p*-nitrobenzoyl substituted imide **15**. Changing the catalyst to $Rh_2(OAc)_4$,

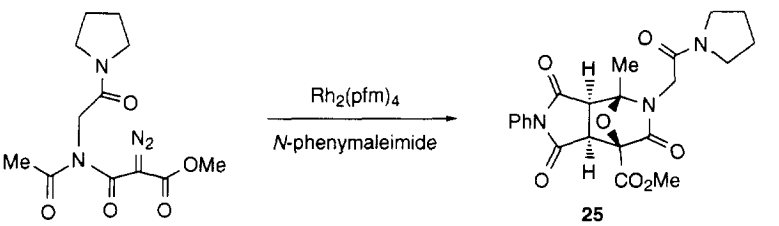


13; R=C_6H_5
14; R=*p*-MeO(C_6H_4)
15; R=*p*-NO_2(C_6H_4)

21; R=C_6H_5
22; R=*p*-MeO(C_6H_4)
23; R=*p*-NO_2(C_6H_4)

however, caused a significant alteration in product distribution. What is so remarkable about this result is the degree to which chemoselectivity of cyclization can be altered by simply changing the ligand group of the catalyst. Moreover, a simplistic rationale based on a "*matched interaction*" of an electrophilic rhodium carbenoid with a nucleophilic carbonyl group does not adequately account for the experimental observations.

The effect of altering the ester carbonyl group in these Rh(II)-catalyzed α-amino ester reactions was next examined. Diazoimide **24** was prepared in good yield by DCC coupling of *N*-acetylglycine with pyrrolidine followed by subsequent malonation and diazo transfer. The rhodium(II) perfluorobutyroamidate-catalyzed reaction of **24** in refluxing benzene with *N*-phenylmaleimide gave the expected isomünchnone cycloadduct **25** in 89% isolated yield. Catalysis by $Rh_2(OAc)_4$, however, led to a complex mixture of products without any

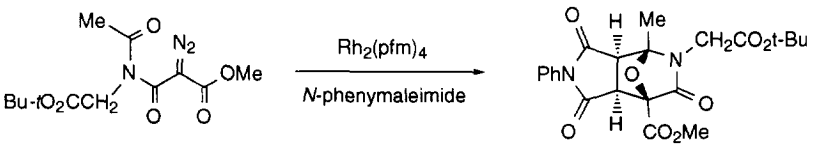


24

25

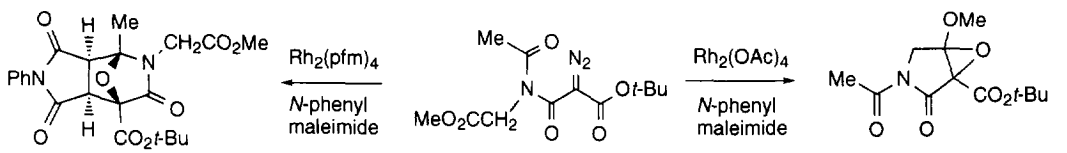
signs of the isomünchnone cycloadduct. In this case, the expected amino-substituted epoxide was presumably too labile to be detected in the crude reaction mixture. Even though we have no definitive evidence for the formation of a transient epoxide from diazoimide **24**, it is clear that the $Rh_2(OAc)_4$-induced reaction proceeds by a different pathway from that encountered with the corresponding perfluorinated catalyst.

A similar tandem cyclization-cycloaddition sequence also occurred with *N*-acetyl-2-diazo-*N*-*t*-butoxycarbonylmethyl malonamic acid methyl ester (**26**). Treatment of **26** with $Rh_2(pfm)_4$ in the presence of *N*-phenylmaleimide resulted in the exclusive formation of isomünchnone cycloadduct **27**. In this case, replacement of the perfluorobutyroamidate ligand with acetate did not alter the course of the reaction, as the isomünchnone cycloadduct **27** was obtained in comparable yield. Apparently, the bulky *t*-butyl ester prevented "*cyclopropanation*" of the adjacent carbonyl π-bond by imposing steric hindrance in the transition state for this reaction. It should be noted that the decomposition of **26** with $Rh_2(OAc)_4$ proceeded more sluggishly than in comparable cases, where epoxide formation occurred easily. This would suggest that isomünchnone formation, while the only viable process, is still not a kinetically attractive pathway with the Rh(II) acetate catalyst.



26 **27**

In order to probe the effect of steric hindrance in the vicinity of the reactive diazo functionality, diazoimide **28** was prepared from di-*t*-butyl malonate in the standard fashion. Once again, the major product obtained from the $Rh_2(pfm)_4$-catalyzed cycloaddition reaction corresponded to the isomünchnone cycloadduct **29**. As before, changing the catalyst to $Rh_2(OAc)_4$ caused a significant alteration in product distribution, resulting in the formation of epoxide **30**. In this case, the bulky *t*-butyl ester group on diazoimide **28** does not impede epoxide formation.



29 **28** **30**

Since the various diazoimides examined in this study show a uniform response to different catalytic systems, it becomes evident that a mechanistic rationale for the chemoselective formation of the five or six-membered ring dipole cannot be based on a static model such as a differing degree of electrophilicity in the respective rhodium(II) carbenoids. The lack of significant substituent effects on the product distribution suggests that the ligand-dependent chemoselectivity between two seemingly similar processes is caused by profound mechanistic differences in their respective reaction pathways. In order to better understand the nature of the ligand effect, we decided to probe whether variations in the solvent polarity or added Lewis acids would affect the chemoselectivity of the reaction.

For this purpose, we examined the reaction of diazoimide **3** with $Rh_2(OAc)_4$ and *N*-phenylmaleimide using a variety of solvents, the results of which are summarized in Table I. Although the reactive nature of the intermediate Rh(II) carbenoid and the lability of the resulting epoxide **9** limit the choice of solvents, some important trends become obvious. While the use of nonpolar solvents such as pentane, benzene, or chloroform led to the formation of epoxide **9**, the isomünchnone cycloadduct **5** was obtained as the sole product with $Rh_2(OAc)_4$ when the highly polar solvent nitromethane was employed. This solvent-dependency indicates that a higher degree of charge separation is involved in the formation of the isomünchnone from the *bona fide* metallo carbenoid compared to the competing epoxide reaction.

The mechanistic picture is accentuated by the effect of an external Lewis acid on the product distribution.[39] Unfortunately, the addition of magnesium bromide or zinc chloride to the $Rh_2(OAc)_4$-catalyzed reaction of diazoimide **3** led to several side reactions of the starting material and/or reaction products, so that no

Table I. Product Distribution in the Rh(II)-Acetate Catalyzed Decomposition of Diazoimide **3**

Entry	Solvent	Epoxide **9**	Isomünchnone Cycloadduct **5**
1	pentane	50%	0%
2	benzene	90%	0%
3	chloroform	90%	0%
4	acetonitrile	0%	50%
5	nitromethane	0%	90%

useful information could be extracted from these experiments. An interesting "*additive effect*" was observed, however, when the reaction was carried out in the presence of 10 mol% of $Sc(OTf)_3$ as the Lewis acid. In this case, 38% of the isomünchnone cycloadduct **5**, in addition to acetate **7** (26%), was obtained (see Scheme I). Neither epoxide **9**, nor the hydroxy enol ether **12** could be detected in the crude mixture. Structure **12** was formed in 74% yield in a control experiment involving the $Sc(OTf)_3$-catalyzed rearrangement of epoxide **9**. Thus, the Lewis acid $Sc(OTf)_3$, which is known to strongly interact with carbonyl groups,[40] exhibited an effect similar to that observed with the polar solvents. More than likely, this involves stabilization of a polar transition state which ultimately results in the formation of the isomünchnone cycloadduct.

The above medium effects clearly demonstrate that epoxide formation from the glycine derived diazo acetamides is a process with comparatively small charge development along the reaction coordinate, and is perfectly consistent with the direct "*cyclopropanation*" mechanism. At the present time, it is not fully understood why isomünchnone formation occurs with all the fluorinated ligands, but only takes place when polar solvents such as nitromethane are used with Rh(II) acetate. It may be that efficient isomünchnone formation requires a temporary change in the coordination sphere of the rhodium dimer. Processes such as partial or complete Rh-O bond cleavage should be feasible for the weakly coordinating perfluorinated ligands but might need solvent or Lewis acid assistance with the acetate group.

In conclusion, we have shown that the product distribution obtained from the Rh(II)-catalyzed decomposition of bifunctional diazoimides can be selectively controlled by the proper choice of catalyst and solvent. The electronic nature of the ligand groups and the polarity of the solvent are the decisive factors, while substrate control by various carbonyl substituents is less important. Isomünchnone formation and subsequent cycloaddition is best accomplished when fluorinated ligands and polar solvents are employed. Experiments to exploit the reaction sequence for stereoselective applications using chiral amino acids are presently underway in our laboratories and will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-hexane mixture as the eluent unless specified otherwise. As a consequence of their lability, the α-diazoimides reported below were characterized by HRMS rather than by

elemental analyses. Due to a very long relaxation time, the resonance for the carbon atom adjacent to the diazo functional group was usually not detected for the diazo compounds prepared in this study.

General Procedure for the Preparation and Rhodium(II)-Catalyzed Reaction of 3-(Acyl-methoxycarbonyl-amino)-2-diazo-3-oxo-propionic Acid Methyl Esters. To a stirred suspension of glycine methyl ester hydrochloride (3.0 g, 24 mmol) in $CHCl_3$ (50 mL) was added Et_3N (6.7 mL, 53 mmol) at 0°C and the mixture was stirred for 5 min at rt. The appropriate acyl chloride (24 mmol) was added dropwise and stirring was continued for 30 min. The solvent was removed under reduced pressure; ethyl acetate (300 mL) was added and the mixture was filtered through a pad of silica gel. Evaporation of the solvent under reduced pressure afforded the amide in high purity. A solution of the *N*-acyl glycine methyl ester (8 mmol) and methyl malonyl chloride (16 mmol) in benzene (30 mL) was heated at reflux for 5 h. The mixture was allowed to cool to rt and Et_3N (16 mmol) was added, followed by ethyl acetate (100 mL) and the suspension was filtered through a pad of silica gel. Evaporation of the solvent under reduced pressure afforded the methyl ester as a clear oil.

To a stirred solution of the above ester (7 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (9.4 mmol) and the appropriate sulfonyl azide (9 mmol). The resulting mixture was stirred at rt for 5 h and then concentrated under reduced pressure to give the diazo ester as a yellow oil. A mixture of the appropriate diazoimide (0.8 mmol), *N*-phenylmaleimide (0.8 mmol), and 1 mg of the rhodium(II) carboxylate catalyst in anhydrous benzene (10 mL) was heated at reflux for 2-6 h. The mixture was cooled to rt and concentrated under reduced pressure to afford the crude product.

3-(Acetyl-methoxycarbonylmethyl-amino)-2-diazo-3-oxo-propionic Acid Methyl Ester (3). The reaction of glycine methyl ester hydrochloride (3.0 g, 24 mmol) and acetyl chloride (2.1 g, 26 mmol) according to the general procedure afforded 3.0 g (96 %) of *N*-acetyl-glycine methyl ester as a white solid; mp 53-55°C (lit.[41] mp 58-59°C). Treatment of this compound (1.0 g, 8 mmol) with methyl malonyl chloride (2.1 g, 16 mmol) according to the general procedure gave 1.66 g (91 %) of 3-(acetyl-methoxycarbonylmethyl-amino)-3-oxo-propionic acid methyl ester (**2**) as a pale yellow oil; IR (neat) 3549, 3012, 1722, 1433, and 1198 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.83 (s, 2H), and 4.48 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.0, 45.6, 46.0, 52.3, 52.6, 167.3, 168.2, 168.5, and 172.3; HRMS Calcd. for $C_9H_{13}NO_6Li$ $(M+Li)^+$: 238.0903. Found 238.0906.

A 1.70 g (7.2 mmol) sample of malonate **2** and methanesulfonyl azide (1.15 g, 9.4 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 1.45 g (79 %) of diazoimide **3** as a bright yellow oil; IR (neat) 2143, 1745, 1674, 1650, and 1311 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H), 2.44 (s, 3H), 3.76 (s, 3H), and 4.37 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.7, 28.4, 47.2, 52.7, 164.2, 168.9, 171.0, and 188.8; HRMS Calcd. for $C_9H_{12}N_3O_6$ $(M+H)^+$: 258.0726. Found: 258.0730.

8-Methoxycarbonylmethyl-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-8-azatricyclo[5.2.1.$0^{2,6}$]-decane-1-carboxylic Acid Methyl Ester (5). A mixture of diazoimide **3** (45 mg, 175 μmol) and *N*-phenylmaleimide (30 mg, 175 μmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was crystallized from EtOAc/hexane to give 64 mg (91 %) of **5** as a white solid,

mp 193-194°C; IR (KBr) 1752, 1716, 1382, and 1114 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.90 (s, 3H), 3.76 (s, 3H), 3.84 (d, 1H, *J* = 6.9 Hz), 3.90 (d, 1H, *J* = 18.3 Hz), 4.00 (s, 3H), 4.10 (d, 1H, *J* = 6.9 Hz), 4.46 (d, 1H, *J* = 18.3 Hz), 7.26 (d, 2H, *J* = 7.2 Hz), and 7.45 (m, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 14.9, 41.3, 48.8, 52.8, 53.3, 54.2, 86.5, 96.5, 126.3, 129.0, 129.2, 131.1, 162.6, 167.3, 168.2, 171.4, and 171.9; Anal Calcd. for $C_{19}H_{18}N_2O_8$: C, 56.72; H, 4.51; N, 6.96. Found: C, 56.44; H, 4.62; N, 6.82.

2-Acetoxy-*N*-methoxycarbonylmethyl-malonamic Acid Methyl Ester (7). To a mixture of diazoimide **3** (75 mg, 0.3 mmol) and 1 mg of rhodium(II) perfluorobutyroamidate in benzene (4 mL) was added 2 drops of water and the mixture was stirred at rt for 18 h. The solvent was removed under reduced pressure. NMR analysis of the crude reaction mixture indicated a 3:1-diastereomeric mixture of 2-hydroxy-3-methoxycarbonylmethyl-2-methyl-4-oxo-oxazolidine-5-carboxylic acid methyl esters (**6**). The major diastereomer exhibited the following properties: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.67 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 3.92 (s, 1H), 4.01 (d, 1H, *J* = 12.0 Hz), 4.11 (d, 1H, *J* = 12.0 Hz), and 4.92 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.2, 41.1, 52.7, 53.9, 76.4, 111.0, 165.3, 167.3, and 169.4. The minor diastereomer showed the following spectral properties: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.74 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 3.85 (s, 1H), 4.01 (d, 1H, *J* = 12.0 Hz), 4.11 (d, 1H, *J* = 12.0 Hz), and 5.03 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.8, 41.2, 53.0, 53.1, 76.0, 111.0, 165.3, 166.9, and 169.4. When the mixture of diastereomers was subjected to flash silica gel chromatography, 61 mg (84 %) of **7** was isolated as a colorless oil; IR (neat) 3367, 1759, 1688, and 1197 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 3.73 (s, 3H), 3.79 (s, 3H), 3.97 (dd, 1H, *J* = 18.3 and 5.1 Hz), 4.09 (dd, 1H, *J* = 18.3 and 5.1 Hz), 5.46 (s, 1H), and 7.10 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 20.3, 41.1, 52.4, 53.2, 72.4, 163.1, 165.8, 168.8, and 169.4; HRMS Calcd. for $C_9H_{14}NO_7$ $(M+H)^+$: 248.0770. Found: 248.0770.

3-Acetyl-5-methoxy-2-oxo-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylic Acid Methyl Ester (9). Treatment of a 70 mg (0.3 mmol) sample of diazoimide **3** with 1 mg of rhodium(II) acetate followed by removal of the solvent left a pale yellow oil whose major constituent (90%) corresponded to epoxide **9** as evidenced by its characteristic spectral data: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.39 (s, 3H), 3.50 (s, 3H), 3.80 (d, 1H, *J* = 12.9 Hz), 3.83 (s, 3H), and 4.14 (d, 1H, *J* = 12.9 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.8, 47.3, 53.5, 54.9, 63.5, 88.8, 161.3, 165.2, and 170.4; HRMS Calcd. for $C_9H_{12}NO_6$ $(M+H)^+$: 230.0665. Found 230.0656.

In addition, small amounts of enol ether **11** were detected in the reaction mixure, but this compound could not be isolated: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 5.14 (s, 1H), 6.15 (s, 1H).

1-Acetyl-3-hydroxy-4,4-dimethoxy-2-oxo-pyrrolidine-3-carboxylic Acid Methyl Ester (10). A sample of epoxide **9**, which was generated from the rhodium(II) acetate decomposition of diazoimide **3**, was dissolved in 10 mL of methanol and one crystal of *p*-TsOH was added. The mixture was stirred at rt overnight, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography to give 60 mg (84 %) of **10** as a white solid, mp 95-96°C; IR (KBr) 3480, 1758, 1730, 1688, and 1047 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.52 (s, 3H), 3.36 (s, 3H), 3.39 (s, 3H), 3.58 (d, 1H, *J* = 12.3 Hz), 3.85 (s, 3H), 3.89 (s, 1H), and 4.13 (d, 1H, *J* = 12.3 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.3, 47.5, 50.2,

51.2, 53.8, 84.0, 100.5, 167.4, 169.3, and 170.5; Anal Calcd. for $C_{10}H_{15}NO_7$: C, 45.98; H, 5.79; N, 5.36. Found: C, 46.20; H, 5.86; N, 5.29.

1-Acetyl-3-hydroxy-4-methoxy-2-oxo-2,3-dihydro-1H-pyrrole-3-carboxylic Acid Methyl Ester (12). A mixture of 110 mg (0.4 mmol) of diazoimide **3** and 1 mg of rhodium(II) acetate in anhydrous benzene (5 mL) was heated at reflux for 1 h. To this mixture was added a 5 mg (0.01 mmol) sample of $Sc(OTf)_3$ and the mixture was heated for an additional 15 min, concentrated under reduced pressure and the residue was subjected to flash silica gel chromatography to give 73 mg (74 %) of **12** as a white solid, mp 120-121°C; IR (KBr) 3331, 3146, 1773, 1752, 1587, 1666, and 1119 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.50 (s, 3H), 3.70 (s, 3H), 3.85 (s, 3H), 4.44 (s, 1H), and 6.69 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.5, 54.3, 57.3, 78.5, 105.0, 144.6, 167.1, 168.5, and 171.1; Anal Calcd. for $C_9H_{11}NO_6$: C, 47.17; H, 4.84; N, 6.11. Found: C, 47.19; H, 4.86; N, 6.08.

3-(Benzoyl-methoxycarbonylmethyl-amino)-2-diazo-3-oxo-propionic Acid Methyl Ester (13). Reaction of glycine methyl ester hydrochloride (2.0 g, 16 mmol) and benzoyl chloride (2.2 g, 16 mmol) according to the general procedure afforded 3.1 g (100 %) of *N*-benzoyl-glycine methyl ester as a white solid; mp 79-80°C (lit.[42] mp 81-82°C). Treatment of this compound (1.7 g, 9.0 mmol) with methyl malonyl chloride (2.4 g, 18 mmol) according to the general procedure gave, after flash silica gel chromatography, 2.07 g (79 %) of the corresponding malonate as a pale yellow oil; IR (neat) 1745, 1695, 1674, 1339, and 1211 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 3.72 (s, 3H), 3.77 (s, 2H), 4.42 (s, 2H), 7.46 (m, 2H), 7.53 (m, 1H), and 7.65 (dd, 2H, J = 8.4 and 1.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 44.6, 48.0, 52.4, 52.5, 128.1, 132.5, 134.1, 167.1, 168.6, 168.7, and 173.0; HRMS Calcd. for $C_{14}H_{16}NO_6$ $(M+H)^+$: 294.0978. Found 294.0967.

A 1.5 g (5 mmol) sample of the above malonate and methanesulfonyl azide (830 mg, 7 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 1.15 g (70 %) of **13** as a viscous yellow oil; IR (neat) 2136, 1709, 1738, 1638, 1439, and 1232 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.60 (s, 3H), 3.76 (s, 3H), 4.60 (s, 2H), 7.44 (m, 3H), and 7.67 (d, 2H, J = 8.4 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 47.5, 52.4, 52.5, 128.2, 129.1, 132.4, 134.8, 165.4, 169.0, and 171.9; HRMS Calcd. for $C_{14}H_{14}N_3O_6$ $(M+H)^+$: 320.0883. Found: 320.0884.

3-[(4-Methoxy-benzoyl)-methoxycarbonyl-amino]-2-diazo-3-oxo-propionic Acid Methyl Ester (14). Reaction of glycine methyl ester hydrochloride (2.0 g, 16 mmol) and 4-methoxy-benzoyl chloride (2.7 g, 16 mmol) according to the general procedure afforded 3.16 g (89 %) of *N*-(4-methoxy-benzoyl)-glycine methyl ester as a white solid; mp 95-97°C (lit.[43] mp 98-99°C). Treatment of this compound (1.0 g, 4.5 mmol) with methyl malonyl chloride (1.2 g, 9 mmol) according to the general procedure gave, after flash silica gel chromatography, 1.17 g (80 %) of the corresponding malonate as a pale yellow oil; IR (neat) 1694, 1604, 1512, 1436, and 1173 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 3.87 (s, 2H), 4.47 (s, 2H), 6.95 (d, 2H, J = 8.8 Hz), and 7.71 (d, 2H, J = 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 44.3, 48.2, 52.4, 52.5, 55.5, 114.3, 126.0, 131.0, 163.4, 168.7, 168.8, and 172.5; HRMS Calcd. for $C_{15}H_{17}NO_7Li$ $(M+Li)^+$: 330.1165. Found: 330.1163.

A 1.0 g (3 mmol) sample of the above malonate and methanesulfonyl azide (500 mg, 4.2 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 0.70 g (64 %) of **14** as a light yellow solid, mp 99-101°C; IR (neat) 2136, 1752, 1725, 1642, 1325, and 1127 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.63 (s, 3H), 3.73 (s, 3H), 3.86 (s, 3H), 4.60 (s, 2H), 6.91 (d, 2H, *J* = 8.8 Hz), and 7.69 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 47.6, 52.4, 52.5, 55.5, 76.6, 113.6, 127.0, 131.4, 155.2, 160.7, 162.9, 165.4, and 169.2; Anal Calcd. for $C_{15}H_{15}N_3O_7$: C, 51.58; H, 4.33; N, 12.03. Found: C, 51.69; H, 4.36; N, 11.93.

3-[Methoxycarbonylmethyl-(4-nitro-benzoyl)-amino]-2-diazo-3-oxo-propionic Acid Methyl Ester (15). Glycine methyl ester hydrochloride (1.0 g, 8 mmol) and *p*-nitro-benzoyl chloride (1.5 g, 8 mmol) were allowed to react according to the general procedure to give 1.5 g (79 %) of *N*-(4-nitro-benzoyl)-glycine methyl ester as a yellow solid; mp 155-157°C (lit.[44] mp 148-151°C). Reaction of this compound (1.0 g, 4.2 mmol) with methyl malonyl chloride (1.15 g, 8.4 mmol) according to the general procedure gave, after flash silica gel chromatography, 0.36 g (26 %) of the corresponding malonate as a yellow oil; IR (neat) 1748, 1704, 1605, 1528, 1439, 1349, and 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H), 3.76 (s, 3H), 3.89 (s, 2H), 4.38 (s, 2H), 7.85 (d, 2H, *J* = 8.7 Hz), and 8.32 (d, 2H, *J* = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 44.4, 47.6, 52.5, 52.7, 124.1, 128.8, 139.8, 149.6, 167.0, 168.2, 168.3, and 171.2; HRMS Calcd. for $C_{14}H_{14}N_2O_8Li$ $(M+Li)^+$: 345.0910. Found: 345.0918.

A 340 mg (1.0 mmol) sample of the above malonate and methanesulfonyl azide (160 mg, 1.35 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 0.24 g (67 %) of **15** as a yellow oil; IR (neat) 2145, 1717, 1527, 1350, and 1234 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.67 (s, 3H), 3.79 (s, 3H), 4.61 (s, 2H), 7.91 (d, 2H, *J* = 8.7 Hz), and 8.27 (d, 2H, *J* = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 29.7, 47.5, 52.7, 77.5, 123.4, 130.1, 140.6, 149.7, 160.4, 165.1, 168.8, and 170.1; HRMS Calcd. for $C_{14}H_{13}N_4O_8$ $(M+H)^+$: 365.0733. Found: 365.0725.

3-(Methoxycarbonyl-methoxycarbonylmethyl-amino)-2-diazo-3-oxo-propionic Acid Methyl Ester (16). Glycine methyl ester hydrochloride (2.0 g, 16 mmol) and methyl chloroformate (1.25 mL, 16 mmol) were allowed to react according to the general procedure to give 2.31 g (97 %) of *N*-(methoxy-carbonyl)-glycine methyl ester[45] which was used in the next step without further purification. Treatment of the carbamate (2.3 g, 15.5 mmol) with methyl malonyl chloride (4.3 g, 31 mmol) according to the general procedure gave, after flash silica gel chromatography, 1.65 g (42 %) of the corresponding malonate as a pale yellow oil; IR (neat) 2255, 1746, 1706, 1443, 1360, 1207, and 1025 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 3.97 (s, 2H), and 4.53 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 44.7, 45.0, 52.1, 52.2, 54.1, 153.7, 167.3, 167.6, and 168.4; HRMS Calcd. for $C_9H_{13}NO_7Li$ $(M+Li)^+$: 254.0825. Found: 254.0848.

A 310 mg (1.3 mmol) sample of the above malonate and *p*-nitrobenzene sulfonyl azide (300 mg, 1.3 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 340 mg (99 %) of **16** as a yellow oil; IR (neat) 2143, 1748, 1652, 1381, and 1014 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), and 4.43 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 46.9, 52.4, 52.5, 54.1, 153.9, 161.2, 164.0, and 168.8; HRMS Calcd. for $C_9H_{12}N_3O_7$ $(M+H)^+$: 274.0675. Found: 274.0670.

8-Methoxycarbonylmethyl-3,5,9-trioxo-4,7-diphenyl-10-oxa-8-azatricyclo[5.2.1.$0^{2,6}$]-decane-1-carboxylic Acid Methyl Ester (17). A mixture of diazoimide **13** (200 mg, 0.6 mmol) and *N*-phenylmaleimide (100 mg, 0.6 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was subjected to flash silica gel chromatography to give 196 mg (70 %) of **17** as a white solid, mp 213-215°C; IR ($CHCl_3$) 1750, 1715, 1386, and 1211 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.33 (d, 1H, *J* = 18.3 Hz), 3.75 (s, 3H), 3.99 (d, 1H, *J* = 6.9 Hz), 4.04 (s, 3H), 4.25 (d, 1H, *J* = 18.3 Hz), 4.81 (d, 1H, *J* = 6.9 Hz), 7.14 (d, 2H, *J* = 6.6 Hz), 7.37 (m, 3H), 7.51 (m, 3H), and 7.75 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 41.6, 49.0, 52.7, 53.4, 86.7, 99.6, 126.2, 127.4, 128.0, 128.7, 128.9, 129.0, 131.1, 131.1, 162.6, 166.5, 168.9, 170.6, and 171.2; Anal Calcd. for $C_{24}H_{20}N_2O_8$: C, 62.07; H, 4.34; N, 6.03. Found: C, 61.81; H, 4.47; N, 5.90.

8-Methoxycarbonylmethyl-7-(4-methoxy-phenyl)-3,5,9-trioxo-4-phenyl-10-oxa-8-azatricyclo-[5.2.1.$0^{2,6}$]decane-1-carboxylic Acid Methyl Ester (18). A mixture of diazoimide **14** (200 mg, 0.6 mmol) and *N*-phenylmaleimide (100 mg, 0.6 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was subjected to flash silica gel chromatography to give 192 mg (68 %) of **18** as a white solid, mp 238-240°C; IR ($CHCl_3$) 2960, 1746, 1719, 1609, 1386, and 1211 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.32 (d, 1H, *J* = 18.2 Hz), 3.74 (s, 3H), 3.84 (s, 3H), 3.98 (d, 1H, *J* = 6.9 Hz), 4.04 (s, 3H), 4.25 (d, 1H, *J* = 18.2 Hz), 4.79 (d, 1H, *J* = 6.9 Hz), 6.99 (d, 2H, *J* = 8.8 Hz), 7.26 (m, 5H), 7.68 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 41.6, 49.1, 52.7, 53.4, 53.4, 55.3, 86.7, 99.7, 114.0, 119.3, 126.3, 128.9, 129.7, 131.2, 161.5, 162.7, 166.5, 168.9, 170.7, and 171.3; Anal Calcd. for $C_{25}H_{22}N_2O_9$: C, 60.73; H, 4.48; N, 5.66. Found: C, 60.58; H, 4.57; N, 5.52.

8-Methoxycarbonylmethyl-7-(4-nitro-phenyl)-3,5,9-trioxo-4-phenyl-10-oxa-8-azatricyclo-[5.2.1.$0^{2,6}$]decane-1-carboxylic Acid Methyl Ester (19). A mixture of diazoimide **15** (150 mg, 0.4 mmol) and *N*-phenylmaleimide (70 mg, 0.4 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was subjected to flash silica gel chromatography to give 140 mg (67 %) of **19** as a white solid, mp 148-149°C; IR ($CHCl_3$) 2925, 1750, 1648, 1386, and 1207 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.29 (d, 1H, *J* = 18.3 Hz), 3.78 (s, 3H), 4.03 (d, 1H, *J* = 6.9 Hz), 4.06 (s, 3H), 4.36 (d, 1H, 18.3 Hz), 4.91 (d, 1H, *J* = 6.9 Hz), 7.25 (m, 5H), 7.99 (d, 2H, *J* = 8.8 Hz), 8.37 (d, 2H, *J* = 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 41.8, 48.7, 53.0, 53.5, 53.6, 86.7, 98.5, 123.8, 126.2, 129.2, 129.6, 130.9, 133.8, 149.5, 162.2, 166.2, 168.8, 170.5, and 170.8; Anal Calcd. for $C_{24}H_{19}N_3O_{10}$: C, 56.59; H, 3.76; N, 8.25. Found: C, 56.45; H, 3.80; N, 8.13.

7-Methoxy-8-Methoxycarbonylmethyl-3,5,9-trioxo-4-phenyl-10-oxa-8-azatricyclo[5.2.1.$0^{2,6}$]-decane-1-carboxylic Acid Methyl Ester (20). A mixture of diazoimide **16** (100 mg, 0.4 mmol) and *N*-phenylmaleimide (64 mg, 0.4 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was subjected to flash silica gel chromatography to give 114 mg (73 %) of **20** as a white solid, mp 130-132°C; IR ($CHCl_3$) 2956, 1757, 1722, 1382, 1218, and 1196 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.69 (s, 3H), 3.78 (s, 3H), 3.87-4.00 (m, 4H), 3.91 (d, 1H, *J* = 6.9 Hz), 4.06 (d, 1H, *J* = 6.9 Hz), 4.31 (d, 1H, *J* = 18.1 Hz), and 7.37 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 41.0, 50.0, 51.4, 52.9,

53.5, 54.6, 84.7, 112.8, 126.4, 128.3, 129.1, 129.2, 131.2, 166.8, 167.7, 169.7, and 171.1; Anal.Calcd. for $C_{19}H_{18}N_2O_9$: C, 54.55; H, 4.34; N, 6.69. Found: C, 54.28; H, 4.40; N, 6.52.

3-Benzoyl-5-methoxy-2-oxo-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylic Acid Methyl Ester (21). Epoxide **21** was obtained (starting from diazoimide **13**) as the major component (85 %) in the reaction mixture when rhodium(II)-acetate was used as the catalyst. The epoxide exhibited the following spectral data: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.62 (s, 3H), 3.87 (s, 3H), 4.21 (d, 1H, J = 12.8 Hz), 4.31 (d, 1H, J = 12.8 Hz), and 7.54 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 48.0, 53.3, 55.0, 63.6, 89.2, 127.9, 128.2, 128.5, 132.4, 164.9, 165.5, and 169.4; HRMS Calcd. for $C_{14}H_{14}NO_6$ $(M+H)^+$: 292.0821. Found 292.0817.

3-(4-Methoxy-benzoyl)-5-methoxy-2-oxo-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylic Acid Methyl Ester (22). Epoxide **22** was obtained (starting from diazoimide **14**) as the major component (85 %) in the reaction mixture when rhodium(II)-acetate was used as the catalyst. The epoxide exhibited the following spectral data: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.63 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 4.26 (d, 2H, J = 2.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), and 7.59 (d, 2H, 8.8 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 48.1, 53.4, 55.0, 89.3, 100.5, 113.3, 113.6, 128.3, 131.4, 148.5, 163.4, and 165.2; HRMS Calcd. for $C_{15}H_{15}NO_7Li$ $(M+Li)^+$: 328.1004. Found 328.1009.

3-(4-Nitro-benzoyl)-5-methoxy-2-oxo-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylic Acid Methyl Ester (23). Epoxide **23** was obtained (starting from diazoimide **15**) as the major component (85 %) in the reaction mixture when rhodium(II)-acetate was used as the catalyst. The epoxide exhibited the following spectral data: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.64 (s, 3H), 3.88 (s, 3H), 4.20 (d, 1H, J = 12.8 Hz), 4.37 (d, 1H, J = 12.8 Hz), 7.67 (d, 2H, J = 8.6 Hz), and 8.24 (d, 2H, J = 8.6 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 47.8, 53.4, 55.1, 63.0, 89.3, 123.2, 128.2, 129.2, 139.0, 160.9, 165.0, and 167.5; HRMS Calcd. for $C_{14}H_{12}N_2O_8Li$ $(M+Li)^+$: 343.0754. Found 343.0746.

***N*-Acetyl-2-diazo-*N*-(2-oxo-pyrrolidin-1-yl-ethyl)-malonamic Acid Methyl Ester (24).** To a stirred suspension of *N*-acetyl glycine (2.0 g, 17 mmol) in CH_2Cl_2 (75 mL) was added DCC (3.6 g, 17 mmol). The mixture was stirred for 1 h at rt and pyrrolidine (1.4 mL, 17 mmol) was added. Stirring was continued for 24 h, the mixture was filtered and the filtrate was concentrated under reduced pressure to give 2.99 g (100 %) of *N*-(2-oxo-2-pyrrolidin-1-yl-ethyl)-acetamide[46] which was used in the next step without purification.

Treatment of a 1.0 g (6 mmol) sample of the above amide with methyl malonyl chloride (1.6 g, 12 mmol) according to the general procedure gave, after flash silica gel chromatography, 1.17 g (73 %) of *N*-acetyl-*N*-(2-oxo-pyrrolidin-1-yl-ethyl)-malonamic acid methyl ester as a yellow oil; IR (neat) 1747, 1713, 1651, 1340, and 1193 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.90 (m, 2H), 2.17 (m, 2H), 2.34 (s, 3H), 3.51 (m, 4H), 3.74 (s, 3H), 3.88 (s, 2H), and 4.46 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.0, 25.2, 26.0, 45.7, 46.1, 46.4, 52.2, 164.9, 167.6, 168.5, and 172.9; HRMS Calcd. for $C_{12}H_{18}N_2O_5Li$ $(M+Li)^+$: 277.1376. Found: 277.1369.

A 1.0 g (4 mmol) sample of the above malonate and methanesulfonyl azide (600 mg, 5 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 0.84 g (76 %) of **24** as a yellow oil; IR (neat) 2140, 1720, 1650, 1438, 1322, 1228, and 1133 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.84 (m, 2H), 2.03 (m, 2H), 2.35 (s, 3H), 3.48 (m, 4H), 3.82

(s, 3H), and 4.47 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.0, 24.2, 26.1, 45.7, 46.0, 47.9, 52.5, 165.4, 165.5, and 172.3; HRMS Calcd. for $C_{12}H_{16}N_4O_5Li$ $(M+Li)^+$: 303.1281. Found 303.1278.

7-Methyl-3,5,9-trioxo-8-(2-oxo-pyrrolidin-1-yl-ethyl)-4-phenyl-10-oxa-4,8-diaza-tricyclo-[5.2.1.0^{2,6}]decane-1-carboxylic Acid Methyl Ester (25). A mixture of diazoimide **24** (200 mg, 0.7 mmol) and *N*-phenylmaleimide (120 mg, 0.7 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was crystallized from EtOAc/hexane to give 266 mg (89 %) of **25** as a white solid, mp 265-267°C; IR ($CHCl_3$) 1713, 1647, 1448, and 1143 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.91 (s, 3H), 1.95 (m, 4H), 3.46 (m, 4H), 3.81 (d, 1H, *J* = 17.2 Hz), 3.88 (d, 1H, *J* = 6.9 Hz), 3.99 (s, 3H), 4.48 (d, 1H, *J* = 17.2 Hz), 4.53 (d, 1H, *J* = 6.9 Hz), and 7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.1, 24.0, 26.1, 42.6, 46.0, 46.2, 49.0, 53.3, 54.4, 86.7, 96.8, 128.9, 129.1, 129.3, 131.3, 163.0, 164.4, 167.7, 171.8, and 172.2; Anal Calcd. for $C_{22}H_{23}N_3O_7$: C, 59.86; H, 5.25; N, 9.52. Found: C, 59.80; H, 5.23; N, 9.46.

***N*-Acetyl-2-diazo-*N*-*tert*-butoxycarbonylmethyl-malonamic Acid Methyl Ester (26).** To a stirred suspension of *N*-acetylglycine (2.0 g, 17.0 mmol) in *t*-BuOAc (50 mL) was added 2 mL of 70 % aqueous $HClO_4$. After stirring for 24 h, the mixture was poured into a saturated solution of $NaHCO_3$ (100 mL) and solid $NaHCO_3$ was added until the solution was neutral. The layers were separated and the aqueous layer was extracted with ether. The combined organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 1.45 g (49 %) of *N*-acetylglycine *tert*-butyl ester[47] which was used directly in the next step.

Treatment of a 1.0 g (6 mmol) sample of the above amino ester with methyl malonyl chloride (1.6 g, 12 mmol) according to the general procedure gave, after flash silica gel chromatography, 1.21 g (76 %) of *N*-acetyl-*N*-*tert*-butoxycarbonylmethyl-malonamic acid methyl ester as a yellow oil; IR (neat) 2982, 1747, and 1372 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 2.30 (s, 3H), 3.74 (s, 3H), 3.86 (s, 2H), and 4.38 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.0, 27.9, 45.7, 46.8, 52.3, 82.9, 167.1, 167.4, 168.2, and 172.4; HRMS Calcd. for $C_{12}H_{19}NO_6Li$ $(M+Li)^+$: 280.1372. Found: 280.1373.

A 1.0 g (4 mmol) sample of the above malonate and *p*-nitrobenzene sulfonyl azide (870 mg, 4 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 920 mg (84 %) of **26** as a yellow oil; IR (neat) 2142, 1724, 1649, 1438, 1371, 1230, and 1158 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 2.32 (s, 3H), 3.82 (s, 3H), and 4.29 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.0, 27.9, 48.1, 52.3, 82.5, 160.8, 165.2, 167.4, and 172.1; HRMS Calcd. for $C_{12}H_{17}N_3O_6Li$ $(M+Li)^+$: 306.1277. Found: 306.1282.

8-*tert*-Butoxycarbonylmethyl-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-8-azatricyclo[5.2.1.0^{2,6}]-decane-1-carboxylic Acid Methyl Ester (27). A mixture of diazoimide **26** (200 mg, 0.7 mmol) and *N*-phenylmaleimide (120 mg, 0.7 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was subjected to flash silica gel chromatography to give 194 mg (66 %) of **27** as a white solid, mp 196-198°C; IR ($CHCl_3$) 2978, 1743, 1717, 1496, and 1150 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 9H), 1.90 (s, 3H), 3.78 (d, 1H, *J* = 18.2 Hz), 3.86 (d, 1H, *J* = 6.9 Hz), 4.00 (s, 3H), 4.18 (d, 1H, *J* = 6.9 Hz), 4.36 (d, 1H, *J* = 18.2 Hz), and 7.35 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.1, 28.0,

42.3, 48.8, 48.9, 53.4, 83.6, 96.6, 126.3, 129.1, 129.2, 131.2, 148.6, 162.7, 166.8, 171.5, and 172.0; Anal Calcd. for $C_{22}H_{24}N_2O_8$: C, 59.45; H, 5.44; N, 6.30. Found: C, 59.54; H, 5.48; N, 6.26.

***N*-Acetyl-*N*-methoxycarbonylmethyl-2-diazo-malonamic Acid *tert*-Butyl Ester (28).** To a solution of di-*tert*-butyl malonate (3.0 g, 14 mmol) in 75 mL of a 4:1 mixture of *t*-BuOH/H_2O was added KOH (0.8 g, 14 mmol). After stirring for 24 h, the mixture was diluted with H_2O, washed with ether, and the aqueous layer was acidified with 10 % HCl and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give 1.32 g of a colorless oil. The oil was dissolved in CH_2Cl_2 (30 mL) and oxalyl chloride (8.25 mL of a 2 M solution in CH_2Cl_2, 16.5 mmol) and 2 drops of DMF were added which resulted in vigorous gas evolution. After stirring for 1 h at rt, the mixture was concentrated under reduced pressure. The resulting acid chloride was added to a solution of *N*-acetylglycine methyl ester (1.0 g, 7.6 mmol) in benzene (30 mL). The mixture was heated at reflux for 5 h, cooled to rt, and Et_3N (6 mL) was added followed by EtOAc. The mixture was filtered through a pad of silica gel (5 cm) and the filtrate was concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 1.3 g (63 %) of *N*-acetyl-*N*-methoxycarbonylmethyl-malonamic acid *tert*-butyl ester as a light orange oil; IR (neat) 2981, 1738, 1438, 1372, and 1216 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 2.32 (s, 3H), 3.77 (s, 2H), 3.78 (s, 3H), and 4.47 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 25.2, 27.9, 46.0, 47.0, 52.6, 82.0, 166.0, 168.6, 168.7, and 172.2; HRMS Calcd. for $C_{12}H_{20}NO_6$ $(M+H)^+$: 274.1291. Found: 274.1298.

A 1.0 g (4 mmol) sample of the above malonate and methanesulfonyl azide (600 mg, 5 mmol) were allowed to react according to the general procedure. The crude product was subjected to flash silica gel chromatography to give 980 mg (90 %) of **28** as a yellow oil; IR (neat) 2141, 1716, 1439, and 1137 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 9H), 2.35 (s, 3H), 3.75 (s, 3H), and 4.42 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.1, 28.1, 47.1, 52.3, 84.1, 159.4, 165.6, 169.0, and 171.9; HRMS Calcd. for $C_{12}H_{18}N_3O_6$ $(M+H)^+$: 300.1196. Found: 300.1191.

8-Methoxycarbonylmethyl-7-methyl-3,5,9-trioxo-4-phenyl-10-oxa-8-azatricyclo[5.2.1.$0^{2,6}$]-decane-1-carboxylic Acid *tert*-Butyl Ester (29). A mixture of diazoimide **28** (200 mg, 0.7 mmol) and *N*-phenylmaleimide (120 mg, 0.7 mmol) was allowed to react with 1 mg of $Rh_2(pfm)_4$ according to the general procedure. The crude residue was subjected to flash silica gel chromatography to give 252 mg (85 %) of **29** as a white solid, mp 172-173°C; IR ($CHCl_3$) 3478, 2982, 1739, 1717, and 1148 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.61 (s, 9H), 1.89 (s, 3H), 3.78 (s, 3H), 3.79 (d, 1H, J = 6.9 Hz), 3.89 (d, 1H, J = 18.3 Hz), 4.07 (d, 1H, J = 6.9 Hz), 4.44 (d, 1H, J = 18.3 Hz), and 7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.0, 28.0, 41.2, 48.4, 52.8, 54.5, 84.8, 96.0, 129.0, 129.2, 129.3, 131.3, 160.9, 167.9, 168.4, 171.3, and 172.0; Anal Calcd. for $C_{22}H_{24}N_2O_8$: C, 59.46; H, 5.44; N, 6.30. Found: C, 59.37; H, 5.48; N, 6.21.

3-Acetyl-5-methoxy-2-oxo-6-oxa-3-azabicyclo[3.1.0]hexane-1-carboxylic Acid *tert*-Butyl Ester (30). Epoxide **30** was obtained (starting from diazoimide **28**) as the major component (90 %) in the reaction mixture when rhodium(II)-acetate was used as the catalyst. The epoxide exhibited the following spectral data: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.56 (s, 9H), 2.48 (s, 3H), 3.58 (s, 3H), 3.89 (d, 1H, J = 13.0 Hz), and 4.20 (d, 1H, J = 13.0 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 24.9, 27.9, 47.5, 54.6, 63.7, 84.9, 88.9, 159.8, 165.8, and 170.5; HRMS Calcd. for $C_{12}H_{17}NO_6Li$ $(M+Li)^+$: 278.1216. Found 278.1202.

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