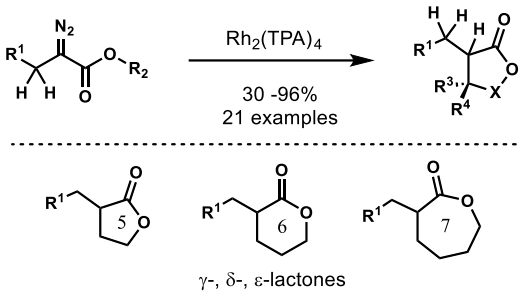
Intramolecular C–H Functionalization of α-Alkyl-α-diazoesters towards the Synthesis of Lactones

Bijaya Bagale, Aubree L. Nolan, Elizabeth U. Heuser, and Jeffrey D. Mighion*

Department of Chemistry and Biochemistry, Kent State University, Kent, Ohio, 44242, United States.

Supporting Information Placeholder

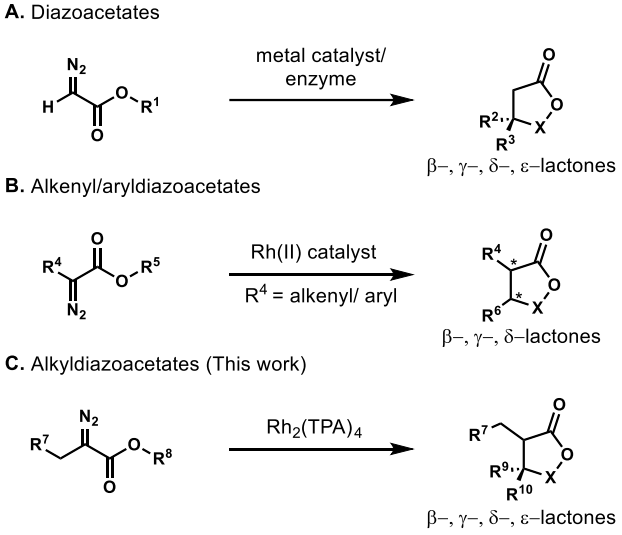


ABSTRACT: Intramolecular C–H functionalization was achieved using rhodium-catalysis with α-alkyl-α-diazoesters. Dirhodium tetratriphenylacetate ($Rh_2(TPA)_4$), a sterically bulky achiral catalyst was found to enable the formation of lactones. Alkyl γ-lactones were synthesized in excellent yields and diastereoselectivity, and a diverse array of disubstituted lactones (γ-, δ-, ε-) were synthesized with good yields and diastereoselectivity. This chemistry was extended to intramolecular C–H insertion in late-stage functionalization with an excellent regio- and diastereoselectivity.

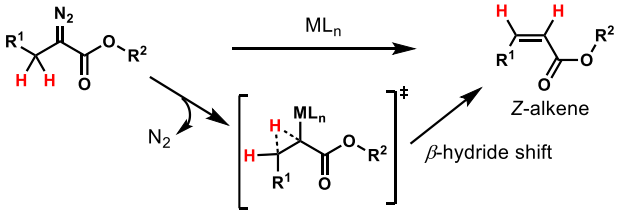
Lactones are cyclic esters that are crucial structural motif across a multitude of areas of chemistry.[1] Lactones have found abundant applications in medicinal chemistry[2], the cosmetic industry[3], and polymer synthesis.[4] While there are numerous synthetic strategies to generate complex lactones,[1-5] C–H functionalization offers a unique, direct access point from simple, readily available alcohols to complex, valuable structures.[6] Diazo compounds, a reactive precursor, along with an appropriate catalyst can perform the intramolecular reaction to give lactones selectively (regio- and stereo-) through the intermediacy of a carbene.

Lactone synthesis the intramolecular C–H functionalization using metal carbenes has been well studied. However, these studies have been limited to diazoacetates[7] and aryl/alkenyldiazoacetates[8] (**Scheme 1A** and **Scheme 1B**). Recently, the Arnold group synthesized a set of diverse lactones using a metal enzyme catalyzed intramolecular functionalization using diazoacetates.[9] Despite this previous work, the use of α-alkyl-α-diazoesters is limited. This is likely due to the unwanted side reaction that generates an alkene via a β-hydride shift (**Scheme 2**).[10,11] Our group has recently synthesized electron deficient α-alkyl-α-diazoesters which slows down this β-hydride migration and may allow for further development of the use of α-alkyl-α-diazoesters.[12] In this work, we demonstrate the ability of these diazoesters to undergo intramolecular C–H insertions using rhodium (II) catalysts to produce lactones in fair to excellent yields with good diasteroselectivity (**Scheme 1C**). We were not only able to synthesize γ-lactones but also lactones of greater ring sizes (δ- and ε-).

Scheme 1. Intramolecular C–H Insertion to Yield Lactones



Scheme 2. Limitation of α-Alkyl-α-diazoesters



https://doi.org/10.26434/chemrxiv-2024-vqk19 **ORCID:** https://orcid.org/0000-0001-6908-5186

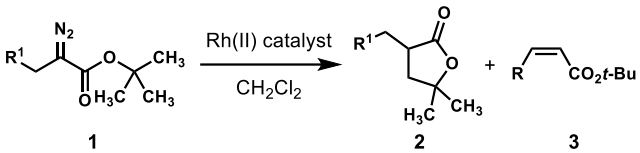
During our cyclopropanation studies of fluorinated diazoacetates, we had observed a lack of selectivity using *tert*-butyl ester substrates.[12] While attempting to understand this lack of selectivity, we observed a very efficient intramolecular C–H insertion of the carbene generated from *tert*-butyl 4,4,4-trifluoro-2-diazobutanoate (**1**) onto the *tert*-butyl ester to give γ-lactone **2**. Our optimal conditions (**Table 1**, entry 1) were at reflux in CH_2Cl_2 with high conversion and very little observed alkene (**3**) formation.

Based on these results, we hypothesized that an electron withdrawing group could inhibit alkene formation and enable lactone formation. This can be further observed in the C–H insertion of diazopropionate which resulted in low conversion and low yield demonstrating the alkyl structure influences reactivity. Also of note, a less sterically encumbered catalyst, ($Rh_2(OAc)_4$), resulted in an increase in the formation of alkene. Our working hypothesis is summarized in **Figure 1**. The conformation of the Rh-carbene is guided by the steric repulsion between the CF_3 group and the catalyst-ligand structure, which limits the overlap of the alkyl C–H bond with the carbene. Also, the electronics of the CF_3 discourage the buildup of positive charge that would occur during the unwanted hydride shift. When the $Rh_2(TPA)_4$ was replaced by $Rh_2(DOSP)_4$, the lactone to alkene ratio was 1: 0.57 (**Table 1**).

With our optimized conditions, γ-lactones were synthesized using various α-alkyl-α-diazoesters with electron withdrawing groups on the alkyl chain (**Scheme 3**). We began with a variety of fluorinated compounds to give lactone products (**2a-d**). While these were high yielding reactions by NMR, but the lactones were co-polar with the catalyst and were difficult to purify. Thus, we then reduced the lactones to diols using lithium aluminum hydride and isolated the diols as a white solids in good yields (60-71%) over two steps (**Scheme 3**). After the successful synthesis of lactones using the fluorinated derivatives, we then changed the electron withdrawing group to an ester. We investigated intramolecular insertions using various ester groups in β-position. We were able to obtain the γ-lactones (**2e-h**) in good to excellent yields (65-85%) (**Scheme 2**). This protocol tolerated numerous esters with the potential for orthogonal functionalization.

We next began to probe esters other than *tert*-butyl groups (**Scheme 4**). Surprisingly, the γ-lactone formed from isopropyl derivative was high yielding (96 %) with a single diastereomer as the major product (**5a**). Both the 3- and 5- substituents in lactone **5a** were cis to each other which was confirmed by *J*-coupling values of the methylene unit between them. This selectivity is hypothesized to arise from the avoidance of a syn-pentane like interaction between the large catalyst and the methyl of the isopropyl group. There was a decrease in yield and higher amounts of alkenes were observed when we moved to a hexyl ester or iso-butyl ester (**5b** and **5c**). Excitingly, a single diastereomer (**5d**) was isolated in good yield (74 %) from the cyclohexyl ester confirmed as the trans-trans isomer by NMR (see SI for details) which likely arises from insertion into an equatorial carbon-hydrogen bond. Both lactones **5e** and **5f** were formed from cyclohexyl 2-diazopropionate, and unlike previous results with a cyclohexyl ester substituent, this reaction resulted in a cis-cis fused ring system as the major product, likely due to the small size of the methyl group allowing the insertion to take place via the chair conformer with the ester in an axial position. A single diastereromer was also observed with the adamantyl chain (**5g**, 32 %) in a lower yield with increased alkene formation, potentially due to the rigidity of the adamantyl group.

Table 1. Deviations from Optimized Condition[a]



entry	Catalyst	R	2:3[b]	Yield (%)[c]
1	$Rh_2(TPA)_4$	CF_3	1:0.01	99
2	$Rh_2(TPA)_4$	H	1:0.16	<10%
3	$Rh_2(OAc)_4$	CF_3	1:1.18	15
4[d]	$Rh_2(S\text{-DOSP})_4$	CF_3	1:0.57	13

[a]Reaction conditions: 0.3 mmol diazo ester in CH_2Cl_2 (1.5 mL) was added dropwise over a period of 1.5 h into the refluxing solution of catalyst (1 mol%) in CH_2Cl_2 (1.5 mL) and refluxed for next 1.5 h, [b]Ratio determined by NMR, [c]NMR yield of lactone **2** measured using trimethoxybenzene as an internal standard, [d]pentane used.

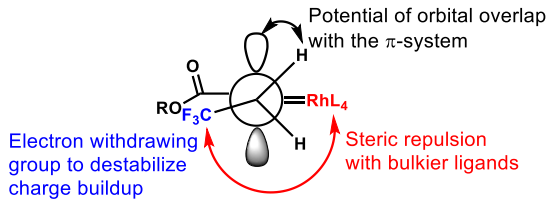
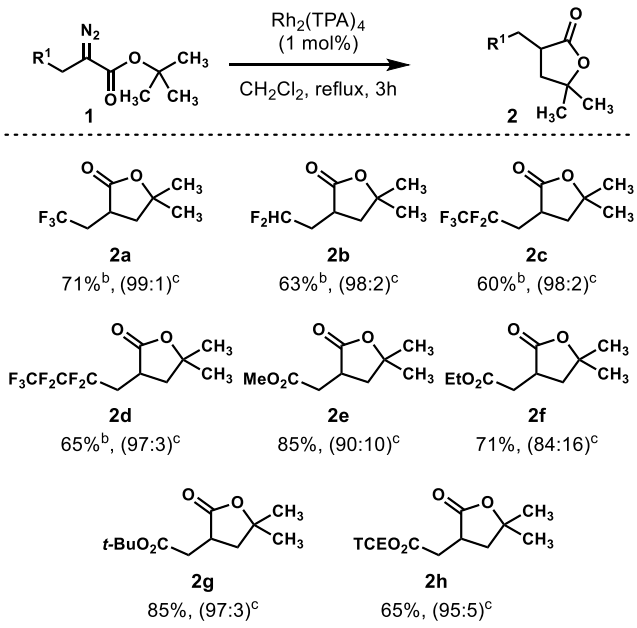


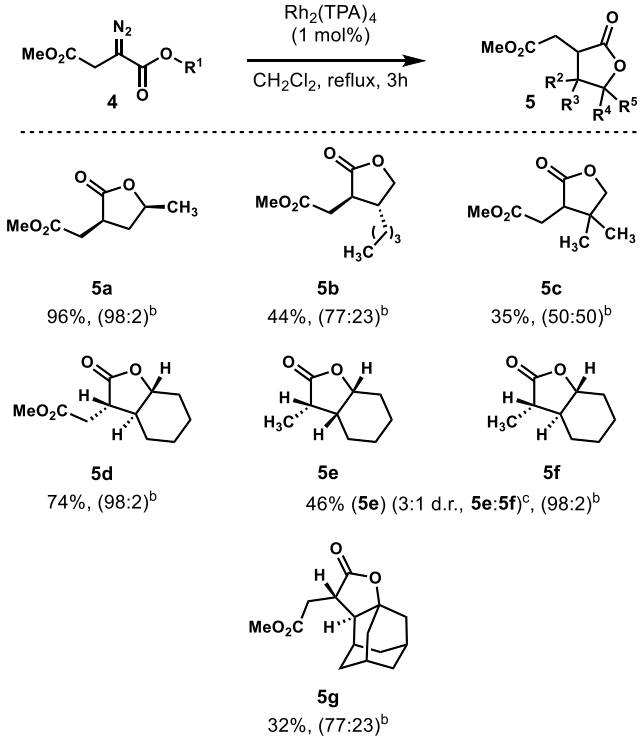
Figure 1. Proposed Newmann Projection for the Metal Carbene with Rationalization for Successful Lactone Synthesis.

Scheme 3: Synthesis of γ-lactones using *tert*-butyl esters[a]



[a]Reactions run on 0.3 scale. Isolated yields. [b]Isolated yield after reduction with $LiAlH_4$. [c]Lactone:alkene ratio determined by crude NMR. TCE = 2,2,2-trichloroethyl.

Scheme 4: Synthesis of substituted γ-lactones[a]

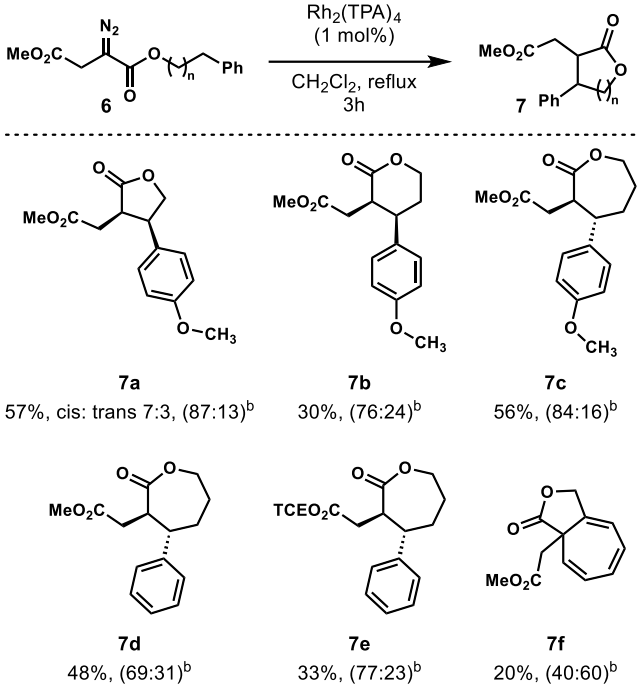


[a]Reactions run on 0.3 scale. Isolated yields. [b]Lactone:alkene ratio determined by crude NMR. [c]Ratio determined by NMR.

We next began to investigate the chemistry of esters with terminal aryl groups with the intention of forming diverse lactones (**Scheme 5**). For the synthesis of these diverse lactones (**7a-f**), the terminal aryl group was anticipated to guide selective insertion into the benzylic position with varying methylene units in the ester chain. Beginning with the γ-lactone system, we obtained γ-lactone **7a** in a moderate yield of 57% with the cis isomer as the major isomer (7:3 dr). Similarly, only the cis-isomer of δ-lactones was isolated from the p-methoxyphenylpropyl ester derivative with a lower yield of 30%. The cis-trans isomer was confirmed by treating the lactone **7b** with DBU which gave a mixture of stereoisomers with an excess of trans lactone with a ratio of 86:14 (trans: cis). We do not currently have a model for this change in diastereoselectivity. However, when ε-lactones were synthesized from phenylbutyl units, only the trans-isomer of the product (**7c-7e**) were obtained. This was confirmed by the *J*-coupling values from ^{1}H-NMR of compound **7e**. Also, the treatment of compound **7c** with DBU gave no change. Lastly, the benzyl ester chain was tested for the formation of β-lactones. However, we obtained the alkene as a major product with a 10 % yield of a γ-lactone (**7f**), a 5,7-bicyclic compound, the product of a Buchner ring expansion of the benzene ring.[13]

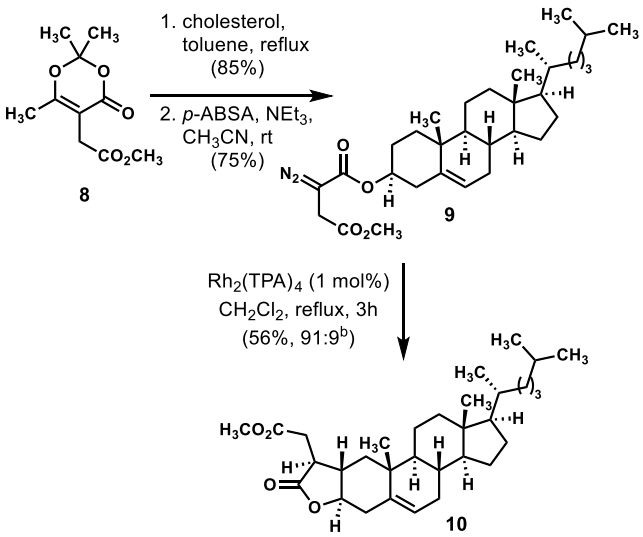
With our understanding from our intramolecular C–H functionalization scope, we looked towards its application in late-stage functionalization. Cholesterol was chosen due to its relative availability and the diazo compound (**9**) was synthesized from two steps starting from dioxanone **8**. A single diastereomeric lactone product (**10**) with a yield of 56 % was achieved. The stereochemistry was confirmed by nOe and *J*-coupling and was shown to match that of cyclohexyl derivative **5d**. The regioselectivity is likely due to the mixture of sterics of the ring junction and relative electronic deactivation by the neighboring sp^2-hybrized carbon as the the equatorial C–H is orthogonal to the π-system.[7e]

Scheme 5: Synthesis of diverse (γ-, δ-, ε-) lactones[a]



[a]Reactions run on 0.3 scale. Isolated yields. [b]Lactone:alkene ratio determined by crude NMR.

Scheme 6: Intramolecular C–H functionalization of cholesterol derivative[a]



[a]Isolated Yields. [b]Lactone:alkene ratio determined by crude NMR.

In conclusion, we have demonstrated intramolecular C–H insertion reactions of electron deficient α-alkyl-α-diazoesters to give diverse lactones with fair to excellent yield. For the synthesis of poly-substituted lactones, the reactions were shown to

be diastereoselective. The trans-isomer for an aliphatic chain and cis-isomer for the aryl group (5- and 6- membered) was favored, whereas the 7-membered lactones were predominantly trans. Also, the late-stage diversification of a natural product derivative was demonstrated to be diastereoselective and regioselective. Further investigations into understanding design principles for the diazoesters and the catalyst for improved yields, enantioselectivity, and expanded substrate scopes are underway.

ASSOCIATED CONTENT

Supporting Information

AUTHOR INFORMATION

Corresponding Author

Jeffrey D. Mighion – Department of Chemistry and Biochemistry, Kent State University, Kent, Ohio, 44242, United States; orcid.org/0000-0001-6908-5186 Email: jmighion@kent.edu

Authors

Bijaya Bagale – Department of Chemistry and Biochemistry, Kent State University, Kent, Ohio, 44242, United States; orcid.org/0009-0001-3424-0761

Aubree L. Nolan – Department of Chemistry and Biochemistry, Kent State University, Kent, Ohio, 44242, United States; orcid.org/0009-0007-7898-6083

Elizabeth U. Heuser – Department of Chemistry and Biochemistry, Kent State University, Kent, Ohio, 44242, United States

Notes

The authors declare no competing financial interest.

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