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# Role of *Ortho*-Substituents on Rhodium-Catalyzed Asymmetric Synthesis of $\beta$-Lactones by Intramolecular C–H Insertions of Aryldiazoacetates

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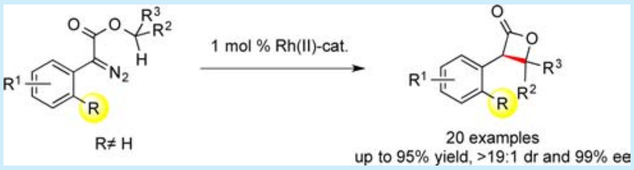
*Supporting Information*

**ABSTRACT:** A rhodium-catalyzed asymmetric synthesis of $\beta$-lactones via intramolecular C–H insertion into the ester group of aryldiazoacetates has been developed. The $\beta$-lactones were synthesized in high yields and with high levels of diastereo- and enantioselectivity. Halo and trifluoromethyl substituents at the *ortho* position of the aryldiazoacetates enhance intramolecular C–H insertions over intermolecular reactions, allowing C–H insertion of even methyl C–H bonds.

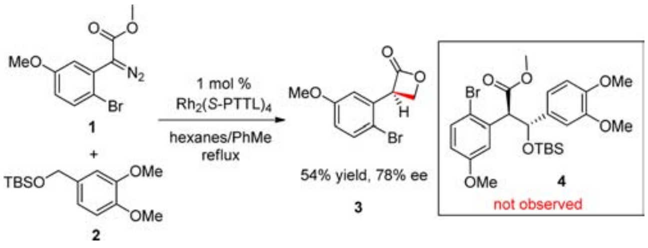


Direct functionalization of C–H bonds represents an area of great interest in organic chemistry and provides new strategies for streamlining the synthesis of natural products and pharmaceuticals.[1] One important type of C–H functionalization is the insertion of a metal-bound carbene into a C–H bond.[2] By exploiting the rhodium-catalyzed decomposition of diazo compounds, the Davies group has developed a number of synthetically useful methods via C–H functionalization with donor/acceptor-substituted metal carbenes.[3] Herein, we report an asymmetric synthesis of $\beta$-lactones via intramolecular insertion of rhodium carbenes into C–H bonds.

$\beta$-Lactones are important organic intermediates and structural motifs in natural products and pharmaceuticals.[4] Thus, developing new methods for the asymmetric synthesis of $\beta$-lactones is desirable.[5] Intramolecular C–H insertion is an attractive strategy for generating lactones and lactams.[6] For the synthesis of lactones, the formation of $\gamma$-lactones is generally preferred over $\beta$-lactones. Aryldiazoacetates have been broadly used in various intermolecular reactions, and Doyle and Che showed that these systems are capable of undergoing intramolecular C–H insertion into methylene or methine C–H bonds to form $\beta$-lactones with modest levels of enantiocontrol (typically <80% ee).[7] In this study we demonstrate that $\beta$-lactone formation can be greatly enhanced by introduction of an *ortho*-substituent on the aryl group of the aryldiazoacetate, enabling C–H functionalization of even relatively unreactive methyl C–H bonds.

The unexpected role of the *ortho*-substituent was discovered during studies on the $Rh_2(S\text{-PTTL})_4$-catalyzed intermolecular C–H insertion reaction between the *ortho*-bromoaryldiazoacetate **1** and the benzyl silyl ether **2** (Scheme 1).[1e] None of the expected intermolecular C–H insertion product **4** was observed. Instead, the $\beta$-lactone product **3** was isolated in 54% yield with 78% ee. Even though we have extensively used methyl aryldiazoacetates in synthesis,[1−3] this was the first time we observed the formation of a $\beta$-lactone, which would require an intramolecular C–H insertion into a methyl C–H bond. The absolute configuration of **3** was unambiguously assigned by X-ray crystallography.[8] Encouraged by this initial discovery, we decided to carry out systematic studies to explore the scope of the $\beta$-lactone synthesis.

**Scheme 1. Discovery of $\beta$-Lactone Formation from Methyl Aryldiazoacetates**



Optimization studies were conducted using aryldiazoacetate **1** as the test substrate with dichloromethane as the solvent (Table 1). Though $Rh_2(S\text{-DOSP})_4$ (Figure 1) is a very effective catalyst in a range of intermolecular C–H insertion reactions,[1−3] it performed relatively poorly in this case, generating the $\beta$-lactone **3** in 31% yield with 51% ee (entry 1). The phthalimido catalysts[9] $Rh_2(S\text{-PTTL})_4$ and $Rh_2(S\text{-PTAD})_4$ gave slightly better results (entries 2 and 3), but the best catalysts were the tetrachlorophthalimido catalysts[10] $Rh_2(S\text{-TCPTTL})_4$ and $Rh_2(S\text{-TCPTAD})_4$ (entries 4 and 5). With $Rh_2(S\text{-TCPTAD})_4$ as the catalyst, the reaction of aryldiazoacetate **1** afforded $\beta$-lactone **3** in 72% yield with 86% ee.

The scope of the intramolecular methyl C–H insertion reaction was then studied using $Rh_2(S\text{-TCPTAD})_4$ as the standard catalyst (Scheme 2). The influence of substituents on

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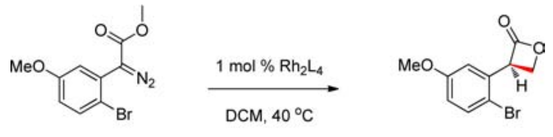
### Table 1. Optimization Studies[a]



**1** **3**

| entry | $Rh_2L_4$ | yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | $Rh_2$(*S*-DOSP)$_4$ | 31 | 51 |
| 2 | $Rh_2$ (*S*-PTTL)$_4$ | 45 | 77 |
| 3 | $Rh_2$ (*S*-PTAD)$_4$ | 23 | 57 |
| 4 | $Rh_2$ (*S*-TCPTTL)$_4$ | 73 | 84 |
| **5** | **$Rh_2$ (*S*-TCPTAD)$_4$** | **72** | **86** |

[a] Standard reaction conditions: **1** (0.5 mmol, 1.0 equiv) in degassed dichloromethane (5 mL) was added to 5 mL of a dichloromethane solution of $Rh_2L_4$ catalyst (0.005 mmol, 1 mol %) at reflux over 3 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

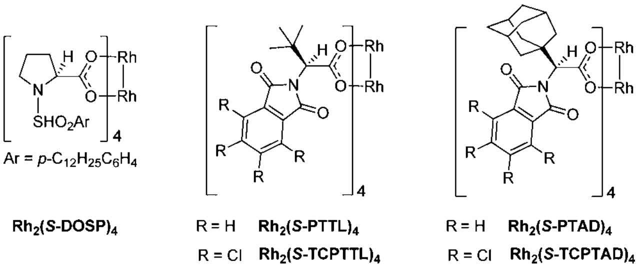
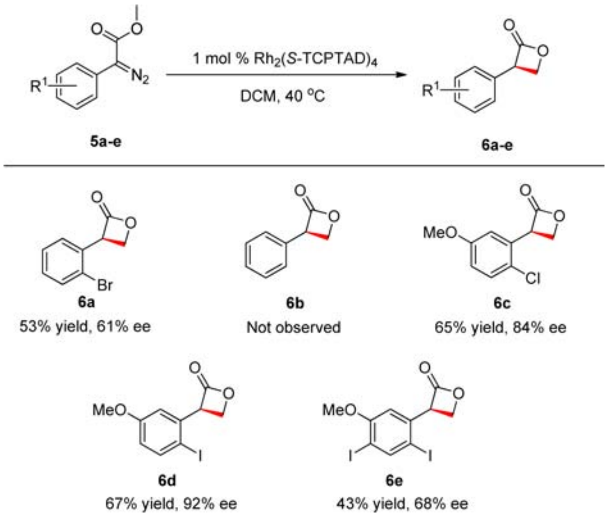


Figure 1. Chiral rhodium catalysts used in this study.

### Scheme 2. Exploration of the Substrate Scope: Methyl C−H Insertions[a]

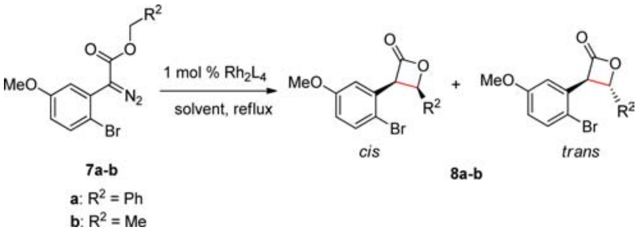


[a] Standard reaction conditions: **5a**−**e** (0.5 mmol, 1.0 equiv) in degassed dichloromethane (5 mL) was added to 5 mL of a dichloromethane solution of the dirhodium catalyst (0.005 mmol, 1 mol %) at reflux over 3 h.

the phenyl ring was first examined. Compared to compound **1**, the reaction of diazo compound **5a** with only an *ortho*-bromo group gave the lactone **6a** in decreased yield and enantioselectivity. The reaction of phenyldiazoacetate **5b**, lacking an *ortho*-substituent, was very informative. None of the *β*-lactone **6b** was formed, demonstrating the importance of *ortho* substitution to enhance intramolecular C−H insertions. Consequently, the influence of other *ortho* substituents was examined. With *ortho*-chloro and iodo groups, lactones **6c** and **6d** were synthesized in good yields and with high levels of enantioselectivity. With an additional iodo group at the *para*-position, compound **6e** was obtained in decreased yield and enantioselectivity. Substrates with *ortho* alkoxy,[3i] carboxylate ester, or nitro groups are not compatible with this chemistry because these groups react with the rhodium carbene. The absolute configurations of *β*-lactones **6a**−**e** were tentatively assigned to be the same as **3** by analogy.

The study was then extended to insertions into methylene C−H bonds. The added stabilization of positive charge built up during the C−H insertion step renders these substrates more reactive. In the presence of $Rh_2$(*S*-TCPTAD)$_4$, the reaction of benzyl ester **7a** produced *cis*-**8a** in good yield with 96% ee and 10:1 dr (Table 2, entry 1). Further studies revealed that the diastereoselectivity can be improved by using $Rh_2$(*S*-TCPTTL)$_4$ as the catalyst. With this catalyst, *cis*-**8a** was obtained in similar yield and enantioselectivity but with >19:1 dr (entry 2). Similar improvement of the diastereoselectivity was observed for the reaction of ethyl aryldiazoacetate **7b**. The diastereoselectivity of lactone *trans*-**8b** was improved from 4:1 to 8.3:1 when the catalyst was changed from $Rh_2$(*S*-TCPTAD)$_4$ to $Rh_2$(*S*-TCPTTL)$_4$ (entries 3 and 4). Interestingly, the reaction of the benzyl aryldiazoacetate **7a** preferentially formed the *cis*-*β*-lactone **8a**, whereas the reaction of the ethyl aryldiazoacetate **7b** preferentially formed the *trans*-*β*-lactone **8b**. The absolute configurations for the major diastereomers *cis*-**8a** and *trans*-**8b** were unambiguously assigned by X-ray crystallography.[11] Because the methylene C−H bond is more reactive than the methyl C−H bond, hydrocarbon solvents can be used without competing intermolecular insertions into the solvent. Slightly higher enantioselectivity for *trans*-**8b** was observed when the reaction of **7b** was performed in refluxing pentane (entry 5), compared to dichloromethane (entry 4).[12]

### Table 2. Optimization of Methylene C−H Insertion

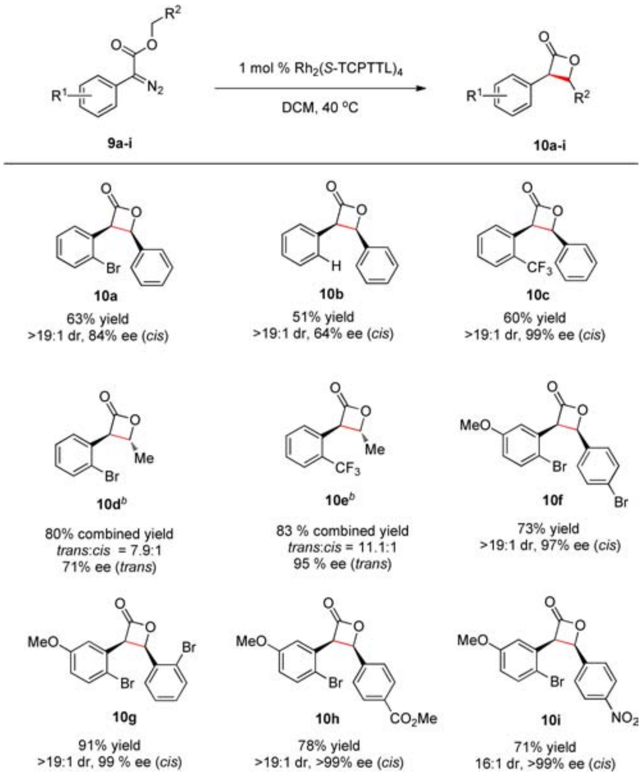


| entry | $R^2$ | $Rh_2L_4$ | solvent | *cis*/*trans*[a] | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | $Rh_2$(*S*-TCPTAD)$_4$ | DCM | 10:1 | 73 | 96 |
| **2** | **Ph** | **$Rh_2$(*S*-TCPTTL)$_4$** | **DCM** | **>19:1** | **72** | **97** |
| 3 | Me | $Rh_2$(*S*-TCPTAD)$_4$ | DCM | 1:4.0 | 78[d] | 82 |
| 4 | Me | $Rh_2$(*S*-TCPTTL)$_4$ | DCM | 1:8.3 | 78[d] | 90 |
| **5** | **Me** | **$Rh_2$(*S*-TCPTTL)$_4$** | ***n*-pentane** | **1:8.3** | **83[d]** | **94** |

[a] Determined by $^1$H NMR analysis of the crude mixture. [b] Isolated yield. [c] Refers to the ee for the major diastereomer. [d] Combined isolated yield.

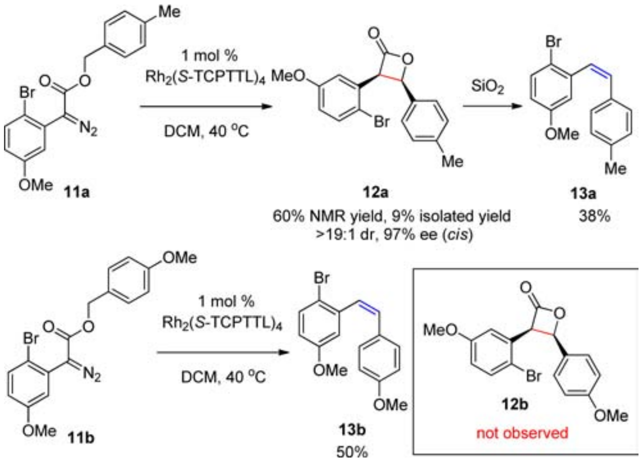
The scope of the methylene C−H insertions was then explored (Scheme 3). It was quickly found that the influence of the *ortho*-substituent is less pronounced in these reactions. The reactions generally proceeded in higher yields and levels of enantioselectivity compared to the methyl C−H insertion reactions. Most notable is the observation that the unsubstituted phenyldiazoacetate **9b** is capable of forming the

### Scheme 3. Exploration of the Substrate Scope: Methylene C–H Insertions[a]

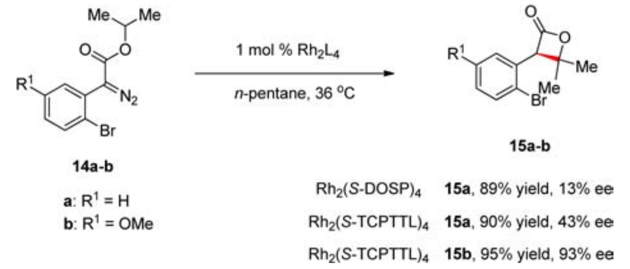


[a]Standard reaction conditions: **9a–i** (0.5 mmol, 1.0 equiv) in degassed dichloromethane (5 mL) was added to a 5 mL dichloromethane solution of the dirhodium catalyst (0.005 mmol, 1 mol %) under reflux over 3 h. [b] *n*-Pentane as the solvent at 36 °C.

### Scheme 4. C–H Insertions of Electron-Rich Benzyl Esters



### Scheme 5. Methine C–H Insertions[a]



[a]Standard reaction conditions: **14** (0.5 mmol, 1.0 equiv) in degassed *n*-pentane (5 mL) was added to a 5 mL *n*-pentane solution of the dirhodium catalyst (0.005 mmol, 1 mol %) at reflux over 3 h.

*β*-lactone **10b** in moderate yield with 64% ee. Benzyl aryldiazoacetates with an *ortho*-substituent are exceptional substrates, generating the *β*-lactones **10c**, **10f–i** with >19:1 dr and 97–99% ee. For the reaction of ethyl aryldiazoacetaes, an *ortho*-trifluoromethyl substituent was also highly favorable and the *β*-lactone **10e** was formed in 83% yield and in 95% ee.

Interestingly, when an electron-donating methyl group was placed at the *para*-position of the benzyl ester (**11a**), the desired C–H insertion product **12a** was isolated in low yield (60% NMR yield). This is because lactone **12a** readily underwent $CO_2$ extrusion to form the olefin **13a** upon column chromatography (Scheme 4). A similar reaction of *β*-silylethyl aryldiazoacetates has been reported previously by our group.[3a] Analysis of the $^1H$ NMR of the crude reaction mixture and HPLC analysis indicated that the diastereoselectivity (>19:1 favoring the *cis* isomer) and enantioselectivity (97% ee) of lactone **12a** were still very high. When the *para*-position of the benzyl ester bears an even stronger electron-donating group, such as the methoxy derivative **11b**, the *β*-lactone **12b** was not observed in the $^1H$ NMR of the crude reaction mixture. Instead, the olefin **13b** was isolated in 50% yield.

The intramolecular insertion into methine C–H bonds of unsubstituted isopropyl phenyldiazoacetate has been previously reported.[6a] The *β*-lactone was obtained in 78% yield with 41% ee when the reaction was performed in refluxing pentane with $Rh_2(S\text{-DOSP})_4$ as the catalyst. Interestingly, the $Rh_2(S\text{-DOSP})_4$-catalyzed reaction of *ortho*-bromo derivative **14a** provided the lactone **15a** with only 13% ee (Scheme 5). Consistent with the methyl and methylene C–H insertions, higher enantioselectivity (43% ee) was observed when $Rh_2(S\text{-TCPTTL})_4$ was used as the catalyst. Further increasing the steric environment around the phenyl group by adding a *meta*-methoxy group (**14b**) improved the yield and enantioselectivity, and lactone **15b** was produced in 95% yield and 93% ee.

In conclusion, the introduction of an *ortho*-substituent on aryldiazoacetates interferes with intermolecular reactions and enhances intramolecular C–H insertions to form *β*-lactones.[13] Even methyl aryldiazoacetates are capable substrates in the formation of *β*-lactones, suggesting that less reactive esters need to be designed to maximize the potential of aryldiazoacetates in intermolecular C–H insertion. In the case of methylene C–H insertions, $Rh_2(S\text{-TCPTTL})_4$ is an exceptional catalyst, resulting in *β*-lactone formation with very high levels of enantio- and diastereoselectivity.

## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(13) During the course of preparation of this manuscript, we became aware of a new paper describing enhanced intramolecular C−H insertions of *ortho*-bromophenyldiazoacetates into methylene and methine bonds using an achiral rhodium acetate catalyst: Wamser, M.; Bach, T. *Synlett* **2014**, 1081.