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Role of *Ortho*-Substituents on Rhodium-Catalyzed Asymmetric Synthesis of β-Lactones by Intramolecular C−H Insertions of Aryldiazoacetates

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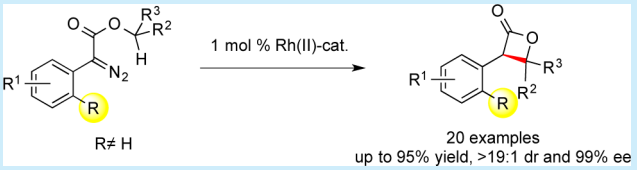
Supporting Information

ABSTRACT: A rhodium-catalyzed asymmetric synthesis of β-lactones via intramolecular C−H insertion into the ester group of aryldiazoacetates has been developed. The β-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.

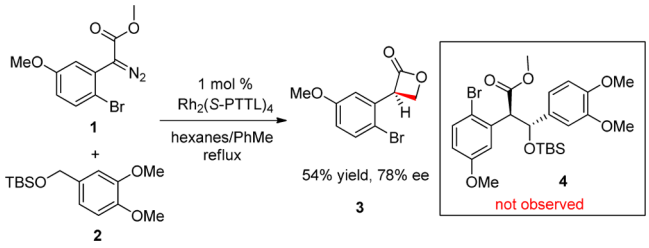


Direct functionalization of C−H bonds represents an area of great interest in organic chemistry and provides new strategies for streamlining the synthesis of natural products and pharmaceuticals.[1] One important type of C−H functionalization is the insertion of a metal-bound carbene into a C−H bond.[2] 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 β-lactones via intramolecular insertion of rhodium carbenes into C−H bonds.

β-Lactones are important organic intermediates and structural motifs in natural products and pharmaceuticals.[4] Thus, developing new methods for the asymmetric synthesis of β-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 γ-lactones is generally preferred over β-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 β-lactones with modest levels of enantiocontrol (typically <80% ee).[7] In this study we demonstrate that β-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*-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 β-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 β-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 β-lactone synthesis.

Scheme 1. Discovery of β-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*-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 β-lactone **3** in 31% yield with 51% ee (entry 1). The phthalimido catalysts[9] Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$ gave slightly better results (entries 2 and 3), but the best catalysts were the tetrachlorophthalimido catalysts[10] Rh_2(*S*-TCPTTL)$_4$ and Rh_2(*S*-TCPTAD)$_4$ (entries 4 and 5). With Rh_2(*S*-TCPTAD)$_4$ as the catalyst, the reaction of aryldiazoacetate **1** afforded β-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*-TCPTAD)$_4$ as the standard catalyst (Scheme 2). The influence of substituents on

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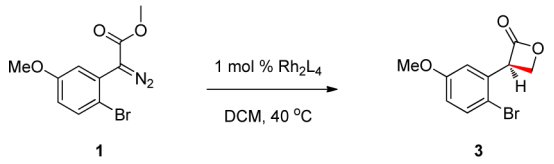
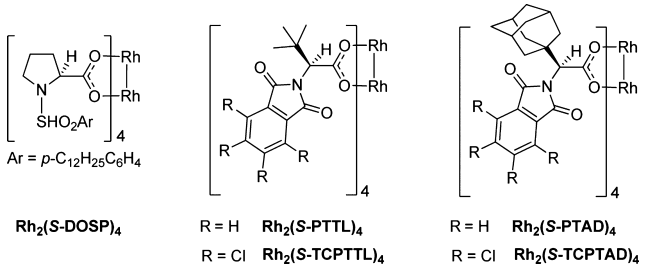
Table 1. Optimization Studies[a]



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**

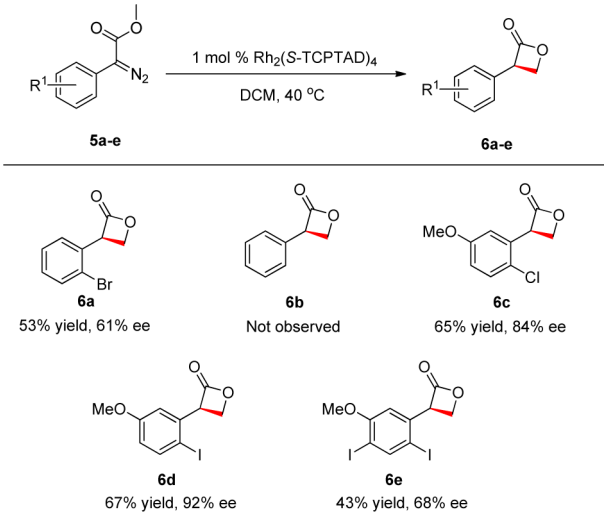
[a]Standard reaction conditions: **1** (0.5 mmol, 1.0 equiv) in degassed dichloromethane (5 mL) was added to 5 mL of a dichloromethane solution of Rh_2L_4 catalyst (0.005 mmol, 1 mol %) at reflux over 3 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis.



Rh_2(*S*-DOSP)$_4$
R = H **Rh_2(*S*-PTTL)$_4$**
R = Cl **Rh_2(*S*-TCPTTL)$_4$**
R = H **Rh_2(*S*-PTAD)$_4$**
R = Cl **Rh_2(*S*-TCPTAD)$_4$**

Figure 1. Chiral rhodium catalysts used in this study.

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

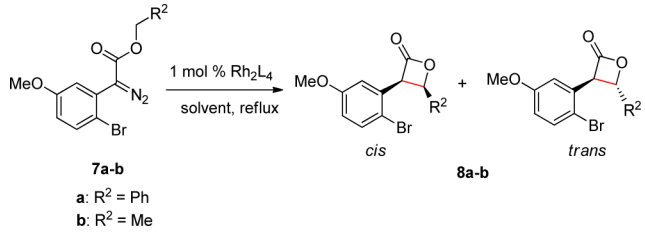


[a]Standard reaction conditions: **5a−e** (0.5 mmol, 1.0 equiv) in degassed dichloromethane (5 mL) was added to 5 mL of a dichloromethane solution of the dirhodium catalyst (0.005 mmol, 1 mol %) at reflux over 3 h.

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

Table 2. Optimization of Methylene C−H Insertion



7a-b
a: R^2 = Ph
b: R^2 = Me

8a-b

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.

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]

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

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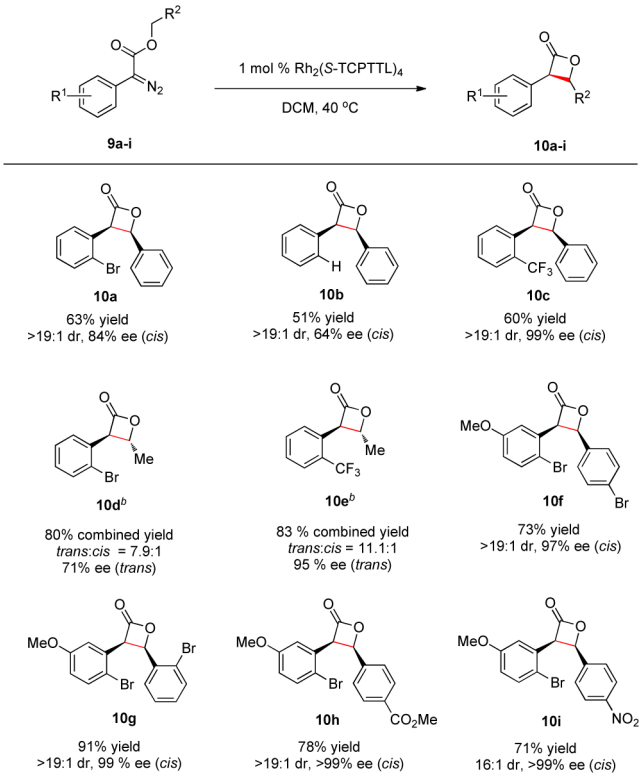
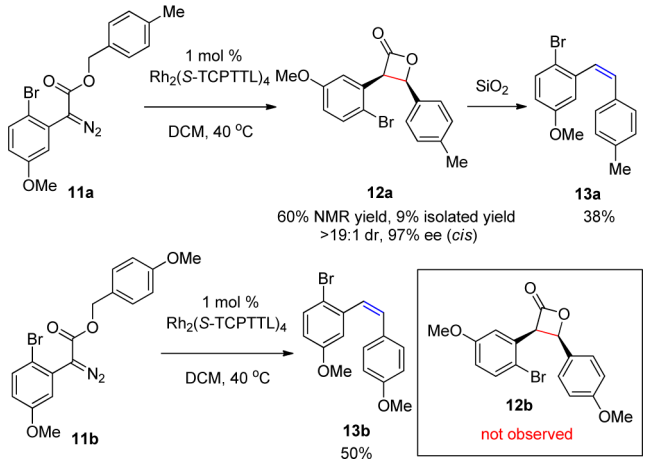
Scheme 3. Exploration of the Substrate Scope: Methylene C−H Insertions[a]

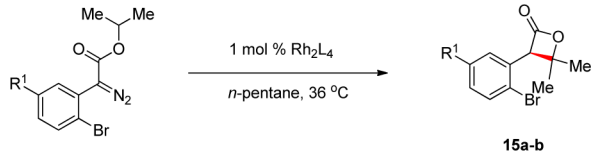


[a]Standard reaction conditions: **9a−i** (0.5 mmol, 1.0 equiv) in degassed dichloromethane (5 mL) was added to a 5 mL dichloromethane solution of the dirhodium catalyst (0.005 mmol, 1 mol %) under reflux over 3 h. [b] *n*-Pentane as the solvent at 36 °C.

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 ^{1}H 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 ^{1}H 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*-DOSP)$_4$ as the catalyst. Interestingly, the Rh_2(*S*-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*-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*-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.

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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.