# Regioselectivity of Intramolecular Rhodium-Catalyzed C–H Insertion Reactions of α-Aryl-α-diazocarboxylates: Influence of the Aryl Substituent

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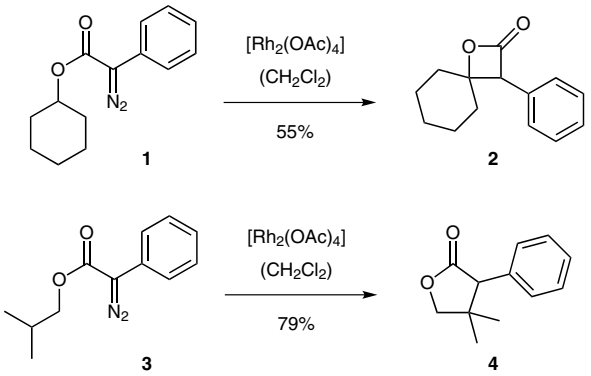
**Abstract:** It was found that α-aryl-α-diazocarboxylates react with variable regioselectivity in intramolecular rhodium-catalyzed C–H insertion reactions. 3-(Trialkoxysilyl)propyl esters underwent a clean *cis*-γ-lactone formation (62–69%) if the aryl rest was a phenyl group while the analogous α-(2-bromophenyl)-α-diazocarboxylates produced the respective β-lactones. In general β-lactone formation was shown to be the only detectable C–H insertion pathway for the latter substrate class irrespective of the ester substituent. The β-lactone products (eight examples) were obtained in yields of 41–68% with a diastereomeric ratio (dr) of 75:25 to 96:4 in favor of the *trans* diastereoisomer. The 2-bromo substituent could be displaced by an aryl group in a subsequent Suzuki cross-coupling reaction.

**Key words:** carbene complexes, diastereoselectivity, insertion, lactones, regioselectivity, rhodium, ring closure

Within the last decades, the intramolecular rhodium-catalyzed C–H insertion reaction of α-diazocarbonyl compounds has been established as a versatile and reliable method to form carbo- and heterocyclic rings.[1] Extensive efforts have been devoted to elucidate the parameters, which control the regioselectivity,[2] the diastereoselectivity[3,4] and the enantioselectivity[1,5] of this transformation. Regarding the regioselectivity, it is generally assumed that insertion occurs into the most electron-rich C–H bond and that the substitution pattern of the substrate therefore influences and possibly alters the regioselectivity. As an example the reaction of α-phenyl-α-diazocarboxylates **1** and **3** is depicted in Scheme 1.[5g] C–H insertion occurs at the tertiary but not at the secondary carbon atom leading in the former case to the formation of β-lactone **2** and in the latter case to the formation of γ-lactone **4**.

Other experiments support this observation, indicating that it is primarily the substitution pattern of the ester bond in α-phenyl-α-diazocarboxylates, which determines the regioselectivity.[6] Although it has been recognized that the substituent at the α-position of an α-diazoketone or an α-diazocarboxylate can increase or decrease the electronic discrimination between different positions,[1,2] an influence of the substitution pattern at the phenyl ring of α-aryl-α-diazocarboxylates has to the best of our knowledge not yet been observed. In this communication we now show, that a 2-bromophenyl substituent in α-position strongly favors the formation of β-lactones upon rhodium-catalyzed dediazotation/C–H insertion of α-aryl-α-diazocarboxylates in benzene solution.




**Scheme 1** Examples of previous work on the rhodium-catalyzed C–H insertion reaction of α-phenyl-α-diazocarboxylates **1** and **3**[5g]

The initial discovery of this selectivity change was made in reactions which aimed at the intermolecular functionalization of hydrocarbons by C–H insertion.[7] While employing 3-(trialkoxysilyl)propyl esters **5** an intramolecular side reaction was observed, which delivered in the absence of a competing intermolecular substrate in good yields the respective lactones **6** as single diastereoisomers (Scheme 2).

The assignment of the relative configuration is based on the coupling constant $^3J$ between the two protons at the stereogenic centers in α- and β-position. For *cis*-configured α-aryl-substituted γ-lactones the coupling constant is typically between 8.0 Hz and 9.0 Hz whereas it is significantly larger for *trans*-γ-lactones ($^3J$ = 10.5–11.0 Hz).[8] For products **6a** and **6b** the relevant coupling constant was found to be identical at $^3J$ = 8.1 Hz. The exclusive formation of the γ-lactones **6** can be tentatively explained by the ability of the silicon–carbon bond to increase the electron density in β-position (β-silicon effect)[9,10] thus rendering the respective methylene group at position C2 of the 3-(trialkoxysilyl)propyl group more reactive. Surprisingly, however, the *ortho*-bromo-substituted analogues **7** of compounds **5** exhibited a completely reversed regioselectivity. The only isolable products of an intramolecular reaction were identified as β-lactones **8**, with a clear preference for the *trans*-products *trans*-**8** over their diaste-

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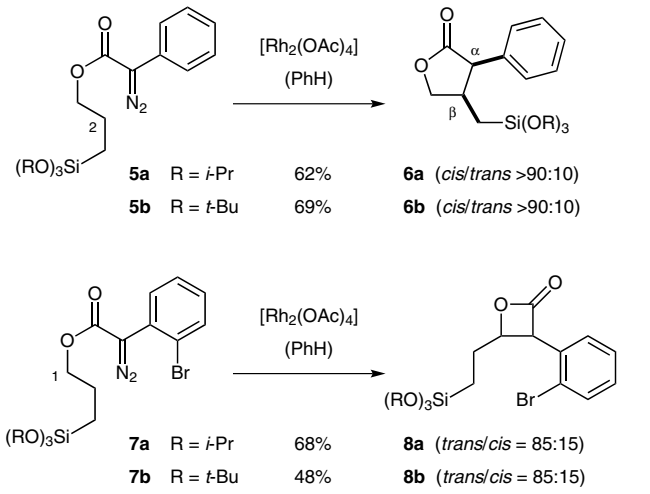



**Scheme 2** Regioselectivity switch upon using a different aryl group in the rhodium-catalyzed C–H insertion reaction of α-aryl-α-diazocarboxylates

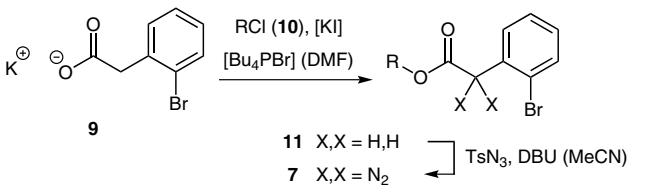
reoisomers *cis*-**8**. Again, the configuration assignment was based on the $^3J$ coupling constants of the hydrogen atoms at the two vicinal stereogenic centers. This value is typically around 4.0 Hz for *trans*-substituted and around 7.0 Hz for *cis*-substituted β-lactones.[11] In our case, the major diastereoisomers obtained from the C–H insertion reaction showed in both cases (**8a** and **8b**) identical coupling constants of $^3J$ = 4.2 Hz. The coupling constant of the minor diastereoisomers was found to be $^3J$ = 6.5 Hz.

In order to explore the scope of the intramolecular C–H insertion of α-(2-bromophenyl)-α-diazocarboxylates, several other members of this compound class were prepared (Table 1). Starting material was in all cases the commercially available 2-bromophenylacetic acid, which was quantitatively converted (KOH, EtOH) into the respective potassium salt **9**. Nucleophilic substitution with an appropriate alkyl chloride **10** delivered the respective esters **11**,[12] which were converted into the desired products by diazotransfer employing *p*-toluenesulfonyl azide ($TsN_3$) as the reagent and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base.[13]

Yields for the combined steps were satisfactory, except for the alkylation reactions with 1,8-dichlorooctane (**10h**), for which an extensive amount of double substitution was observed. The reaction was not further optimized. Alcohol **10f** was prepared from silyl ether **10g** (see footnote c of Table 1).

The rhodium-catalyzed reaction of α-diazocarboxylates **7** delivered under standard conditions (Scheme 3) the respective β-lactones in moderate to good yields (41–66%).[14] Even with primary alkyl groups a clear preference for the formation of the *trans* product was observed, which varied from 75:25 to 93:7. The isopropyl-substituted product **8d** could not be isolated in pure form. The reaction remained incomplete and the starting material (**7d**) was not fully separable from the product. In addition, reduced diazo compound, i.e. 2-bromophenylacetate **11d**,

**Table 1** Preparation of α-(2-Bromophenyl)-α-diazocarboxylates **7** from Potassium 2-Bromophenylacetate (**9**)



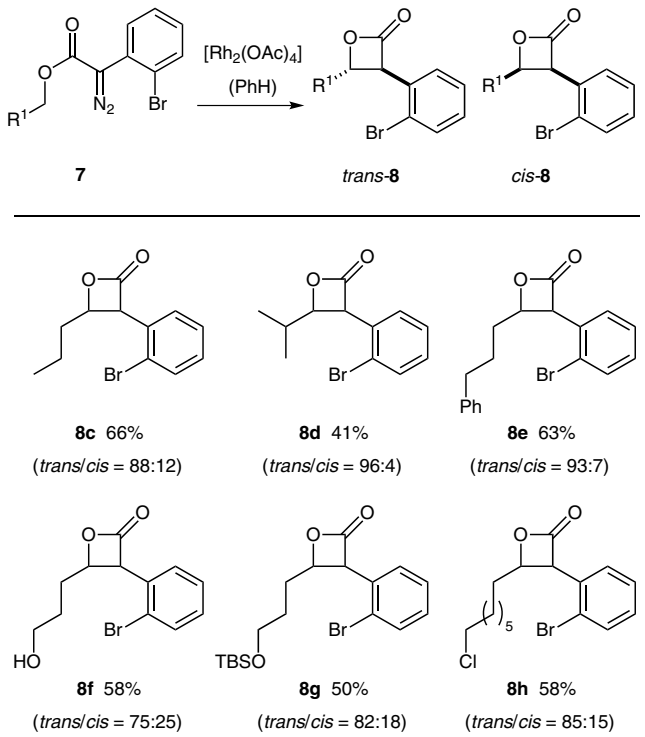

| Alkyl chloride | (**10**) | Yield of **11** (%)[a] | Yield of **7** (%)[b] |
|---|---|---|---|
| (*i*-PrO)$_3$SiO | **10a** | 62 | 75 |
| (*t*-BuO)$_3$SiO | **10b** | 78 | 77 |
| | **10c** | 66 | 86 |
| | **10d** | 60 | 68 |
| Ph | **10e** | 63 | 87 |
| HO | **10f** | – | –[c] |
| TBSO | **10g** | 35 | 69 |
| Cl | **10h** | 12[d] | 72 |

[a] The alkylation reaction was performed at 120 °C in DMF using potassium acetate **9** (1.2 equiv). KI (10 mol%) and tetrabutylphosphonium bromide (2 mol%) were employed in catalytic amounts. The given yield refers to isolated product.
[b] The diazotransfer was performed with stoichiometric amounts of $TsN_3$ (1.0 equiv) and an excess of DBU (1.5 equiv). The given yield refers to isolated product.
[c] The compound was obtained by desilylation of silyl ether **10g** with tetrabutylammonium fluoride (TBAF) in THF (55% yield).
[d] Two-fold substitution was observed as a competing side reaction (23%). In addition, 39% of unreacted starting material was recovered.

was identified as a by-product. The respective γ-lactone could neither be detected nor isolated. The same holds true for the other products **8**, which were obtained as mixtures of *trans*- and *cis*-diastereoisomers and which showed no indication of γ-lactone formation. In some of the reactions impurities resulting from non-converted starting material could not be completely removed.

In order to possibly distinguish between the electronic and steric influence of the phenyl substitution pattern in α-aryl-α-diazocarboxylates, other members of this compound class were prepared. If the aryl group was 2-methylphenyl (Figure 1, compound **12**) a sluggish reaction was observed under the typical reaction conditions given in Scheme 3 [*c* = 0.5 M; 80 °C in benzene; 0.5 mol% $Rh_2(OAc)_4$]. It was possible to identify β-lactone **13** in the product mixture but the compound could not be isolated in pure form. The yield was determined by integration of appropriate $^1$H NMR signals in a purified substrate/product mixture. The result with the 3-bromophenyl derivative was very similar. Minor amounts of the β-lactone could be identified but yields remained low (<20%). The 4-bromophenyl derivative **14** did not deliver any β-lactone. The




**Scheme 3** Formation[a] of β-lactones **8** by rhodium-catalyzed intramolecular C–H insertion reactions of α-(2-bromophenyl)-α-diazocarboxylates **7**. [a] The reaction was performed by addition of a solution of substrate **7** in benzene ($c$ = 0.5 M) to a solution of 0.5 mol% catalyst in benzene at 80 °C. The diastereomeric products **8** were not separable and the ratio of diastereoisomers was determined by $^1$H NMR spectroscopy.

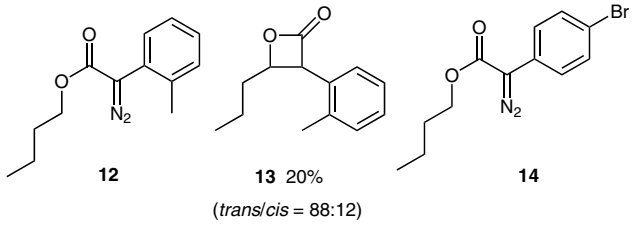
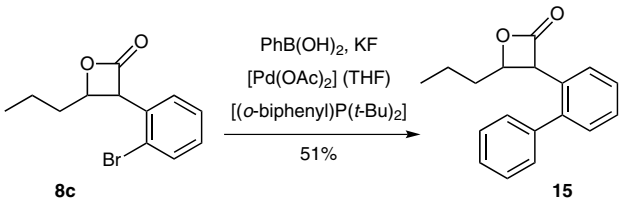



**Figure 1** Structures of butyl α-aryl-α-diazocarboxylates **12**, **14** and of β-lactone **13**

only product derived from the diazo compound was the respective dimer as a *cis*-/*trans*-mixture. In general, apart from dediazotation of the starting material the formation of dimers (aryl-substituted fumarates and maleates) was the major side reaction to be observed in competition with the desired cyclization.

In a short series of experiments it was investigated whether the bromine substituent in products **8** can be replaced by an aryl group in a Suzuki cross-coupling reaction. Initial attempts using phenylboronic acid in combination with $Pd(OAc)_2$, various ligands and bases were not successful. Decomposition was observed, which was partially attributed to the sensitivity of the lactone ring towards basic conditions. Better results were achieved when employing potassium fluoride as an additive. With 2-biphenyl-di-*tert*-butylphosphane as ligand and $Pd(OAc)_2$ as palladium source[15] there was a notable conversion at 50 °C (Scheme 4) and bromide **8c** delivered the desired product **15** in 51% yield. The starting material was used as 88:12 mixture of *trans*- and *cis*-isomer. Surprisingly, the product showed four sets of signals in its NMR spectra, pairs of which integrated to a ratio of 88:12. It seems likely that the restricted rotation around a C–C single bond is responsible for the second pair of signals.




**Scheme 4** Palladium-catalyzed Suzuki cross-coupling of aryl bromide **8c** with phenylboronic acid

Mechanistically, there is no stringent hypothesis, which explains the influence of the *ortho*-bromo substituent. As evident from Scheme 2, the change in regioselectivity is very pronounced but the effect is neither solely steric nor solely electronic (Figure 1). Synthetically, the exclusive formation of β-lactones is useful in particular because further bromide substitution reactions are feasible.

## Acknowledgment

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**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are procedures and analytical data for all new compounds.

**Primary Data** for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0057th. FIDs and associated files for the $^1$H and $^{13}$C NMR spectra for compounds **5**, **6**, **7**, **8**, **11**, and **15** are provided.

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(14) **Representative Procedure for 8c**: A 50-mL Schlenk flask was charged with benzene (12 mL) and $Rh_2(OAc)_4$ (0.5 mol%) and the solution was heated to 80 °C. Diazo compound **7c** (567 mg, 1.91 mmol), dissolved in benzene (4.0 mL), was added to the catalyst solution at 80 °C over 3 h employing a syringe pump. After complete addition the reaction mixture was stirred at 80 °C for additional 30 min. After removing the solvent under reduced pressure the crude reaction mixture was purified directly by flash column chromatography (silica gel, pentane–EtOAc 98:2 → 90:10) yielding compound **8c** (340 mg, 1.26 mmol, 66%) as an inseparable mixture of diastereoisomers in a ratio of 88:12 (*trans*/*cis*). $^1$H NMR: (360 MHz, $CDCl_3$): δ = 0.91 [t, $^3J$ = 7.4 Hz, 0.36 H, Me (*cis*)], 1.00 [t, $^3J$ = 7.4 Hz, 2.64 H, Me (*trans*)], 1.32–1.40 [m, 0.24 H, C$H_2$CH$_3$ (*cis*)], 1.49–1.65 [m, 1.76 H, C$H_2$CH$_3$ (*trans*)], 1.93–2.01 (m, 1 H, CHCH$_2$CH*H*), 2.12–2.21 (m, 1 H, CHCH$_2$C*H*H), 4.43–4.47 [m, 0.88 H, C*H*CH$_2$ (*trans*)], 4.80 [d, $^3J$ = 4.3 Hz, 0.88 H, C*H*Ar (*trans*)], 4.89–4.93 [m, 0.12 H, C*H*CH$_2$ (*cis*)], 5.26 [d, $^3J$ = 6.6 Hz, 0.12 H, C*H*Ar (*cis*)], 7.14 [virt. t, $^3J \cong$ 7.4 Hz, 0.12 H, CCH$_{ar}$C*H*$_{ar}$ (*cis*)], 7.21 [virt. t, $^3J \cong$ 7.4 Hz, 0.88 H, CCH$_{ar}$C*H*$_{ar}$ (*trans*)], 7.28 [virt. t, $^3J \cong$ 7.4 Hz, 0.12 H, CCH$_{ar}$CH$_{ar}$C*H*$_{ar}$ (*cis*)], 7.36 [virt. t, $^3J \cong$ 7.4 Hz, 0.88 H, CCH$_{ar}$CH$_{ar}$C*H*$_{ar}$ (*trans*)], 7.44 [d, $^3J$ = 7.8 Hz, 0.88 H, CC*H*$_{ar}$ (*trans*)], 7.48 [d, $^3J$ = 7.8 Hz, 0.12 H, CC*H*$_{ar}$ (*cis*)], 7.57 [d, $^3J$ = 7.8 Hz, 0.12 H, C*H*$_{ar}$CBr (*cis*)], 7.60 [d, $^3J$ = 7.8 Hz, 0.88 H, C*H*$_{ar}$CBr (*trans*)]. $^{13}$C NMR (90.6 MHz, $CDCl_3$): δ (major diastereoisomer) = 13.7, 18.4, 30.6, 60.8, 80.1, 123.8, 128.3, 128.7, 129.9, 133.0, 133.2, 168.8. HRMS: *m*/*z* calcd for $C_9H_6{}^{79}BrO_2$: 224.0195; found: 224.0191. HRMS: *m*/*z* calcd for $C_9H_6{}^{81}BrO_2$: 226.0175; found: 226.0177.

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