

Enantioselective β -Lactone Formation from Phenyl diazoacetates via Catalytic Intramolecular Carbon-Hydrogen Insertion

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Abstract: Dirhodium(II) catalysts with chiral carboxylate or carboxamidate effectively promote β -lactone formation from phenyl diazoacetates in high yield and with up to 63% ee.

Key words: enantioselective carbon-hydrogen insertion, chiral dirhodium(II) catalysts, phenyl diazoacetates, β -lactones

Dirhodium(II) catalyzed intramolecular carbon-hydrogen insertion reactions originating with diazocarbonyl compounds have enjoyed wide popularity for the synthesis of cycloalkanones, lactones, and lactams.¹⁻⁴ They exhibit a high preference for the formation of five-membered rings and, in the absence of conformational restrictions,⁵ reactivity follows the order tertiary > secondary >> primary.⁶ There are few examples of insertion reactions favoring ring sizes other than five in these reactions,^{1,7-9} even when electronic influences would justify them.¹⁰ Recently, Davies and coworkers have demonstrated that aryldiazoacetates exhibit much higher levels of selectivity in C-H insertion reactions.¹¹ Based on this report and other indicators of reactivity/selectivity,¹ we have searched for carbon-hydrogen insertion reactions that could provide the formation of four-membered ring β -lactones in reasonable yields and with catalyst-directed enantiocontrol.

The first substrate tested was isopropyl phenyl diazoacetate, and we were surprised to find that the corresponding β -lactone was virtually the sole product in reactions that were catalyzed by rhodium acetate and by dirhodium(II)

compounds **4** and **5** (Table 1). Here, insertion into the 3 °C-H bond was favored over insertion into one of six 1 °C-H bonds despite the additional strain introduced by formation of a four- rather than a five-membered ring. Traces of **3**, mainly the *trans*-disubstituted lactone, were observed, but the overall difference in reactivity could be estimated to be greater than 50:1. Products were identified by spectroscopic analysis with reference to literature reports of the same compounds.¹²

Table 1 Enantioselectivity in Carbon-Hydrogen Insertion Reactions of Isopropyl Phenyl diazoacetate^a

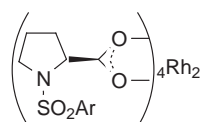
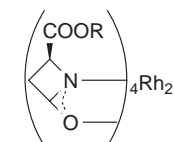
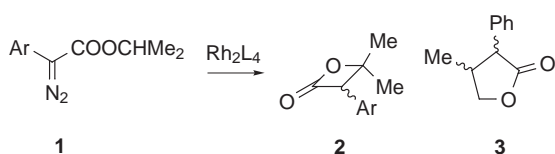
| catalyst | yield, % ^b | ee, % ^c |
|--|-----------------------|--------------------|
| | 2 (Ar = Ph) | 2 (Ar = Ph) |
| Rh ₂ (OAc) ₄ | 84 | — |
| Rh ₂ (<i>S</i> -MEAZ) ₄ (4a) | 83 | 33 |
| Rh ₂ (<i>S</i> -IBAZ) ₄ (4b) | 79 | 26 |
| Rh ₂ (<i>S</i> -BNAZ) ₄ (4c) | 66 | 30 |
| Rh ₂ (<i>S</i> -CHAZ) ₄ (4d) | 85 | 35 |
| Rh ₂ (<i>S</i> -NEPAZ) ₄ (4e) | 84 | 24 |
| Rh ₂ (<i>S</i> -DOSP) ₄ (5) | 86 | 36 |
| Rh ₂ (<i>S</i> -DOSP) ₄ (5) ^d | 78 | 41 |

^a Reactions were performed in refluxing CH₂Cl₂, unless specified otherwise, using 1.0 mol% of catalyst. ^b Yield of product after separation of catalyst (up to 70% yield after chromatographic purification).

^c Enantiomer separation and analyses were performed on a 25-cm, 4.6-mm (*R,R*)-WHELK-O column using 5% EtOAc in hexanes (8.2 and 9.0 min for the individual enantiomers). ^d Reaction performed in refluxing pentane.

Reactions catalyzed by chiral dirhodium(II) compounds, either the Rh₂(*S*-DOSP)₄ catalyst of Davies⁴ or our own chiral azetidinone-ligated catalysts,^{13,14} generally resulted in β -lactone product in high yield but with only modest enantioselectivities. The use of Rh₂(*S*-DOSP)₄ produced product with the highest% ee value, especially when the reaction was performed in pentane. Reactions with azetidinone-ligated catalysts in pentane provided no obvious advantages over reactions performed in CH₂Cl₂.

An attempt was made to determine the electronic influence of aryl substituents from aryldiazoacetates on enantiocontrol. However, significantly lower product yields were obtained with Ar = *p*-MeOC₆H₄ – a substituent that, based on published reports by Davies,^{11,15,16} we thought would lead to modest changes in enantioselectivity,% ee



4a: R = Me, Rh₂(4*S*-MEAZ)₄

4b: R = ^tBu, Rh₂(4*S*-IBAZ)₄

4c: R = Bn, Rh₂(4*S*-BNAZ)₄

4d: R = *c*C₆H₁₁, Rh₂(4*S*-CHAZ)₄

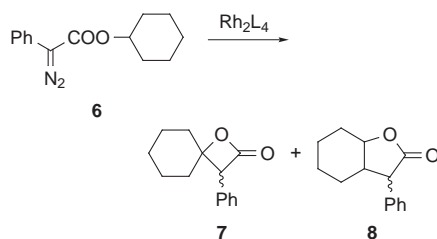
4e: R = CH₂CMe₃, Rh₂(4*S*-NEPAZ)₄

5: Ar = *p*-C₁₂H₂₅C₆H₄, Rh₂(*S*-DOSP)₄

Scheme 1

values were considerably lower than those reported in Table 1 (33% ee with **5**). However, with Ar = *p*-MeC₆H₄, Rh₂(*S*-DOSP)₄ gave the corresponding β-lactone in 77% yield with 48% ee, but Rh₂(*S*-MEAZ)₄ gave product in lower yield (34%) and with lower enantioselectivity (27% ee). The reason for this apparent discrepancy is as yet unresolved.

Diazo decomposition of cyclohexyl diazoacetate produces the γ-lactone products virtually exclusively.⁷ The corresponding β-lactone, if formed at all, is a very minor product. In contrast, diazo decomposition of cyclohexyl phenyldiazoacetate **6** gives the corresponding β-lactone product **7**¹⁷ with near exclusivity (Table 2), and the catalyst had virtually no influence on regioselectivity. Here, enantioselectivities were higher than those obtained with isopropyl phenyldiazoacetate. Comparable results were obtained with *cis*-4-methylcyclohexyl phenyl-diazoacetate [with Rh₂(4*S*-MEAZ)₄ in CH₂Cl₂: 74% yield, 44% ee; with Rh₂(*S*-DOSP)₄ in pentane: 56% yield, 44% ee].



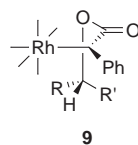
Scheme 2

Table 2 Enantioselectivity and Regioselectivity in Carbon-Hydrogen Insertion Reactions of Cyclohexyl Phenyldiazoacetate^a

| catalyst | yield, % ^b | ee, % ^c | |
|--|-----------------------|--------------------|-------------------------|
| | | 7 | 7:8 ^d |
| Rh ₂ (OAc) ₄ | 55 | — | 98:2 |
| Rh ₂ (<i>S</i> -MEAZ) ₄ (4a) | 67 | 50 | 98:2 |
| Rh ₂ (<i>S</i> -IBAZ) ₄ (4b) | 66 | 51 | 97:3 |
| Rh ₂ (<i>S</i> -NEPAZ) ₄ (4c) | 65 | 42 | 97:3 |
| Rh ₂ (<i>S</i> -DOSP) ₄ (5) | 52 | 49 | 98:2 |
| Rh ₂ (<i>S</i> -DOSP) ₄ (5) ^d | 69 | 63 | 98:2 |

^a Reactions were performed as described in Table 1. ^b Product yield after separation of catalyst (up to 53% yield of **7** after chromatographic purification). ^c Enantiomer separation and analyses were performed on a 25-cm, 4.6-mm (R,R)-WHELK-O column using 5% EtOAc in hexanes (8.2 and 9.1 min for the individual enantiomers). ^d Determined by ¹H NMR of unique spectral regions for **7** (ref. 17) and **8** (ref. 18). ^e Reaction performed in refluxing pentane.

In each C–H insertion reaction presented thus far the chiral center that is generated is the original diazo-carbon atom with a probable transition state orientation that is depicted in **9**. When reactions of **1**, **6**, and their analogs R and R' are identical and, if insertion occurs as shown in **9**,



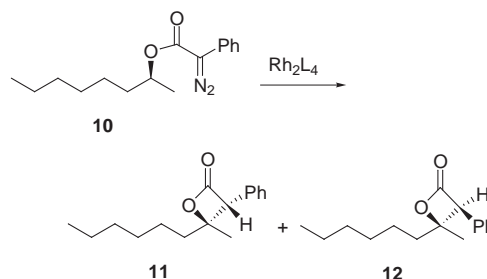
the configuration of the β-lactone product would be *R*. When R and R' are not identical, one can expect a diastereomeric product distribution that reflects the relative stabilities of attached carbene/catalyst configuration. This is effectually represented in results from diazo decomposition of (*S*)-(+)-2-octyl phenyldiazoacetate (**10**) from which two diastereomeric β-lactone products (**11** and **12**)¹⁹ are formed in good yields (Table 3). γ-Lactone products were, at best, trace constituents of the reaction mixture. As expected, changing catalyst configurations, Rh₂(4*S*-MEAZ)₄ and Rh₂(4*R*-MEAZ)₄, resulted in modest, but measurable, differences in diastereoselection indicative of match/mismatch in catalyst-substrate interactions. Surprisingly, the **11:12** ratio with Rh₂(*S*-DOSP)₄ was opposite to that with the 4*S*-azetidinone-ligated dirhodium(II) catalysts, and the reason for this is unknown.

Table 3 Diastereoselectivity in Carbon-Hydrogen Insertion Reactions of (*S*)-(+)-2-Octyl Phenyldiazoacetate^a

| catalyst | yield, % | ee, % |
|---|-----------------------------|---------------------------|
| | 11 + 12 ^b | 11:12 ^c |
| Rh ₂ (OAc) ₄ | 91 ^d | 37:63 |
| Rh ₂ (<i>S</i> -MEAZ) ₄ (4a) | 79 | 22:78 |
| Rh ₂ (<i>R</i> -MEAZ) ₄ (<i>ent</i> - 4a) | 60 | 53:47 |
| Rh ₂ (<i>S</i> -IBAZ) ₄ (4b) | 68 | 36:64 |
| Rh ₂ (<i>S</i> -DOSP) ₄ (5) ^e | 56 | 69:31 |

^a Reactions were performed as described in Table 1. ^b Yield after removal of catalyst. ^c Determined by ¹H NMR analysis and confirmed by GC on a SPB-5 column operated at 100 °C. ^d Column chromatography on silica (2.5–10% EtOAc in hexanes) allowed isolation of **11** (28% yield) and **12** (57% yield) as separate products. ^e Reaction performed in refluxing pentane.

Overall, dirhodium(II) catalysts are surprisingly selective



Scheme 3

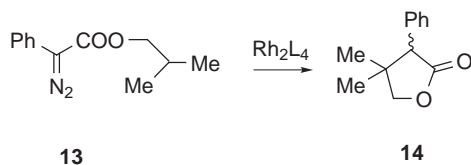
for β-lactone formation, affording these products in high

yield, although with modest enantiocontrol. However, when a tertiary C–H bond is available that could result in a γ -lactone product, as is the case with isobutyl phenyl diazoacetate (**13**), only the γ -lactone product is observed (Table 4). Here use of the chiral azetidinone-ligated catalysts gave comparable % ee values for the insertion product (**14**) to results from $\text{Rh}_2(\text{S-DOSP})_4$ in pentane. Clearly, the presence of a tertiary C–H bond directs C–H insertion with phenyl diazoacetates to a far greater extent than that found with diazoacetates alone.

Table 4 Enantioselectivity in Carbon-Hydrogen Insertion Reactions of Isobutyl Phenyl diazoacetate^a

| catalyst | yield, % 14 ^b | ee, % 14 ^c |
|--|------------------------------------|---------------------------------|
| $\text{Rh}_2(\text{OAc})_4$ | 79 | — |
| $\text{Rh}_2(\text{S-MEAZ})_4$ (4a) | 94 | 90 |
| $\text{Rh}_2(\text{S-IBAZ})_4$ (4b) | 89 | 84 |
| $\text{Rh}_2(\text{S-DOSP})_4$ (5) | 95 | 56 |
| $\text{Rh}_2(\text{S-DOSP})_4$ (5) ^d | 89 | 86 |

^aReactions were performed as described in Table 1. ^bYield after of removal of catalyst. ^cAnalysis on a WHELK-O column using 20% EtOAc in hexanes. ^dReaction performed in pentane.



Scheme 4

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References and Notes

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- (19) Diastereoisomers were separated, and they were identified by spectral methods; assignments were based on nOe experiments.

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