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

<table>
<thead>
<tr>
<th>catalyst</th>
<th>yield, %b</th>
<th>ee, %c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh2(OAc)2</td>
<td>84</td>
<td>—</td>
</tr>
<tr>
<td>Rh2(S-MEAZ)4</td>
<td>83</td>
<td>33</td>
</tr>
<tr>
<td>Rh2(S-IBAZ)4</td>
<td>79</td>
<td>26</td>
</tr>
<tr>
<td>Rh2(S-BNAZ)4</td>
<td>66</td>
<td>30</td>
</tr>
<tr>
<td>Rh2(S-CHAZ)4</td>
<td>85</td>
<td>35</td>
</tr>
<tr>
<td>Rh2(S-NEPAZ)4</td>
<td>84</td>
<td>24</td>
</tr>
<tr>
<td>Rh2(S-DOSP)4</td>
<td>86</td>
<td>36</td>
</tr>
<tr>
<td>Rh2(S-DOSP)4d</td>
<td>78</td>
<td>41</td>
</tr>
</tbody>
</table>

* Reactions were performed in refluxing CH2Cl2, unless specified otherwise, using 1.0 mol% of catalyst. 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 Davies8 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 = o-MeOC6H4 — a substituent that, based on published reports by Davies,11,15,16 we thought would lead to modest changes in enantioselectivity, % ee
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. The corresponding γ-lactone, if formed at all, is a very minor product. In contrast, diazo decomposition of cyclohexyl phenyldiazoacetate gives the corresponding γ-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.

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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 phenyldiazoacetate (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 Rh₂(S-DOSP)₄ in pentane. Clearly, the presence of a tertiary C–H bond directs C–H insertion with phenyldiazoacetates to a far greater extent than that found with diazoacetates alone.

Table 4 Enantioselectivity in Carbon-Hydrogen Insertion Reactions of Isobutyl Phenyldiazoacetate

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield, %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(OAc)₄</td>
<td>79</td>
<td>–</td>
</tr>
<tr>
<td>Rh₂(S-MEAZ)₄ (4a)</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>Rh₂(S-IBAZ)₄ (4b)</td>
<td>89</td>
<td>84</td>
</tr>
<tr>
<td>Rh₂(S-DOSP)₄ (5)</td>
<td>95</td>
<td>56</td>
</tr>
<tr>
<td>Rh₂(S-DOSP)₄ (5')</td>
<td>89</td>
<td>86</td>
</tr>
</tbody>
</table>

*a Reactions were performed as described in Table 1. † Yield after removal of catalyst. ‡ Analysis on a WHELK-O column using 20% EtOAc in hexanes. ‡ Reaction performed in pentane.

Scheme 4

Acknowledgement

Support for this research from the National Science Foundation and from the National Institutes of Health (GM-46503) is gratefully acknowledged. We are grateful to Professor Huw M. L. Davies for providing us with a generous sample of Rh₂(S-DOSP)₄. This letter is dedicated to Professor Ryogi Noyori, whose insightful contributions to the development of asymmetric catalysis for metal carbene transformations has led us to fruitful discoveries.

References and Notes

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

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