Asymmetric Cyclopropanations and Cycloadditions of Dioxocarbenes

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Received 16 February 2006

Abstract: Methods for enantioselective transfer of carbenes starting from precursors carrying two carbonyl groups have been elaborated. A one-pot procedure for olefin cyclopropanation with CH-acidic precursors via intermediate phenyliodonium ylides has been developed. The reaction involves the transition-metal-induced decomposition of a diazo compound to afford an intermediate metallocarbone, which subsequently transfers the carbene moiety to an appropriate substrate. The enantioselectivity of the reaction may be controlled by the chiral ligands surrounding the metal. Exceptional enantioselectivities have been reported for asymmetric transfer of diazoacetate esters 1a and amidines 1b, having a single substituent on the diazo group. In contrast, the enantioselectivity of diazo compounds carrying two substituents of type 2 and 3 is more difficult to control (Figure 1). A notable exception to this is provided by vinyl- and aryl-substituted diazo esters 2c and 2d, respectively, with which impressive selectivities have been achieved.1 Davies proposed that the unusual selectivity of the metallocarbenes derived from these latter precursors should be ascribed to a transition state occurring late on the reaction coordinate, as evidenced by the high negative p-value of −1.0 for cyclopropanation of styrene with Rh(II) catalysts.2

In contrast, diazo esters having a second electron-withdrawing substituent such as diazomalonate (2a) or 2-diazodimedone (3a) exhibit low selectivity. The corresponding metallocarbenes are highly electrophilic, and the transition state for carbene transfer occurs early on the reaction coordinate. Typically, a p-value of −0.3 has been reported for cyclopropanation of styrene with diazomalonate 2a. In addition, the steric requirements of disubstituted carbenes differ obviously from those of their mono-substituted counterparts, so that the need for different catalysts is not surprising.

This paper summarizes efforts which we have carried out during the past years with the objective to tune Rh(II) catalysts in order to achieve enantioselective carbene transfer with diazo esters carrying a second electron-attracting substituent 2a, 2b, 3 and 4 (Figure 1) or the corresponding phenyl iodonium ylides. Alternatively, vinyl diazoacetates were used as synthetic equivalents of diazoacetates in cyclopropanations and formal cycloadditions.

A One-Pot Carbene Transfer with in situ Generated Phenyliodonium Ylides

The transition-metal-catalyzed decomposition of dimethyl diazomalonate (2a, X = CO$_2$Me) and of the diazo derivative of Meldrum’s acid 3b presents difficulties owing to the high stability of the diazo precursors. In addition, the carbene transfer is characterized by disappointingly low enantioselectivities.3 Phenyl iodonium ylides derived from CH-acidic compounds may be used as substitutes for diazo compounds in catalytic carbene-transfer reactions,6 in analogy to phenyliodonium ylides derived from carbamates, sulfonamides, and sulfamates (iminophenyliodanes) which may be applied to catalytic nitrene transfer.7 The ylide 5 derived from Meldrum’s acid is isolable and decomposes under mild conditions in the presence of Rh(II) catalysts, but the reactions proceed with only modest enantioselectivity.8 In general, however, such ylides are amorphous, often unstable and difficult to purify. Protocols for in situ generation and decomposition of iminophenyliodanes have been developed which offer significant improvement over procedures using isolable ylides.9 Based on previous work of Dauban,10 and in parallel with Charette,11 we have adapted the in situ procedure for carbene transfer with dimethyl malonate (7) and

SYNTHESIS 2006, No. 10, pp 1689–1696
Advanced online publication: 27.04.2006
DOI: 10.1055/s-2006-926452; Art ID: C00206SS
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Meldrum’s acid 9. The intermediate ylides 8 and 5, respectively, were generated either with iodosylbenzene (PhI=O) in the presence of MgO and molecular sieves (for 7), or with diacetoxyiodobenzene [PhI(OAc)2] in the presence of aluminum oxide and molecular sieves (for 9). Good yields of cyclopropanes 11 were obtained when the reaction was carried out with a tenfold excess of olefin (Scheme 1). In addition, an unexpected substituent effect on the enantioselectivity was observed when Rh(II)-based catalysts (Figure 2) with 4-substituted 1,8-napthanoyl-de-rivatized tert-leucine ligands were screened. The ee for cyclopropanation of styrene (6a) with 7 increased from 37% with [Rh2{(S)-nttl}4] to 82% with [Rh2{4-Br-(S)-nttl}4] (Table 1). This compares favorably with the 40% ee reported for cyclopropanation of styrene with dimethyl diazomalonate in the presence of Doyle’s [Rh2{(S)-bnaz}4] catalyst. [Rh2{(S)-nttl}4]-catalyst is particularly adapted for diazo transfer with the TIPS-enol ether 13 derived from methyl diazoacetoacetate (2b).

Cyclopropanation with Methyl (Silyloxyvinyl)diazooacetate 13

The decomposition of diazoacetoacetates (2b) results in the formation of carbenes which are destabilized by two electron withdrawing carbonyl substituents and which are, therefore, unselective. (Silyloxyvinyl)diazoacetates, their synthetic equivalents, have been used with some success by Davies for enantioselective carbene transfer with [Rh2{(S)-dosp}4] as catalyst. We observed that the [Rh2{(S)-nttl}4]-catalyst is particularly adapted for diazo transfer with the TIPS-enol ether 13 derived from methyl diazoacetoacetate (2b).

Cyclopropanation of Styrene 14

The cyclopropanation of styrene (6a) with methyl diazooacetate (2b) in the presence of [Rh2{(S)-nttl}4] proceeded in 68% yield to a mixture of racemic trans-adduct 12 and enanto-enriched cis-12 of 16% ee in a 1:8 ratio (Scheme 2). Replacement of 2b by its silyl enol ether 13 resulted in a dramatic increase in selectivity. Under optimized conditions [Rh2{(S)-nttl}4] afforded the cis isomer of the adduct 14a with 95% diastereoselectivity and 95% diastereomeric purity.

Figure 2 Structures of some rhodium catalysts

enantioselectivity at –78 °C in toluene (Table 2). The absolute configuration of 14a was determined to be 1R,2S by X-ray crystallography. Lower selectivities were observed, when the TIPS group was replaced by the sterically less demanding TBDMS.

Surprisingly, when 2-bromostyrene (6g) was cyclopropanated with 13 and [Rh2((S)-nttl)4] as catalyst, the resulting cyclopropane 14g had an ee of only 11%. In contrast, the 2-methyl derivative 6h reacted normally with...
91% ee. The 4-bromo substituted styrene 6b, in turn, reacted with an enantioselectivity of 92%, while the selectivity of the 4-chloro and the 4-methoxy derivatives were found in the same range with 94% and 89%, respectively. These observations may be rationalized by formation of a (achiral) intermediate bromonium ylide 15, which transfers the carbene moiety intramolecularly to the ortho-double bond without intervention of the chiral catalyst. In contrast, the high enantioselectivity of the cyclopropane 14b derived from 4-bromostyrene suggests the intervention of the catalyst in the transfer of the carbene moiety of the (hypothetical) ylide 16.

Treatment of 14a with TBAF afforded the methyl ketone trans-17 (61%), while its ozonolysis led to the half-ester 18 (16%). Thus, the two-step procedure allows the stereospecific introduction of a cyclopropane carrying two different carbonyl substituent with high enantioselectivity.

Intramolecular Cyclopropanation of Allyl 2-Diazo-3-silyloxybut-3-enoates 19

The intramolecular cyclopropanation of (silyloxyvinyl) diazoacetates, i.e. allyl 2-diazo-3-silyloxybut-3-enoates 19 was somewhat less successful. The diazo precursors 19a–c were synthesized by conventional procedures and subjected to diazo decomposition with a limited selection of catalysts (Scheme 3 and Table 3). The cyclopropanation product of 19c underwent Cope rearrangement under the reaction conditions to afford 22. The enantioselectivities of all these reactions were below those achieved with styrene. [Rh₂{(S)-nttl}₄] and [Rh₂{(S)-pttl}₄] provided the best selectivities, although even at –78 °C the highest ee was only 89%. Surprisingly, Davies’ [Rh₂{(S)-dosp}₄] catalyst was less suitable for these transformations, although it has been found to be the catalyst of choice in other intramolecular cyclopropanations of allyl diazoacetates.

The absolute configurations of 20a and 22, were determined by degradation with O₃ to afford 21 and 23, respectively, of known absolute configuration. The absolute configuration of 20b, in turn, was tentatively assigned on

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**Table 3** Intramolecular Cyclopropanation of Allyl 2-Diazo-3-silyloxybut-3-enoates 19a–c in Toluene

<table>
<thead>
<tr>
<th>Precursor R</th>
<th>Catalyst</th>
<th>Product, yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19a H</td>
<td>[Rh₂{(S)-nttl}₄]</td>
<td>20a, 81</td>
<td>47³</td>
</tr>
<tr>
<td>19a H</td>
<td>[Rh₂{(S)-pttl}₄]</td>
<td>20a, 75</td>
<td>50⁴</td>
</tr>
<tr>
<td>19a H</td>
<td>[Rh₂{(S)-pttl}₄]</td>
<td>20a, 50</td>
<td>70⁴</td>
</tr>
<tr>
<td>19b Ph</td>
<td>[Rh₂{(S)-nttl}₄]</td>
<td>20b, 77</td>
<td>73⁴</td>
</tr>
<tr>
<td>19b Ph</td>
<td>[Rh₂{(S)-pttl}₄]</td>
<td>20b, 93</td>
<td>77³</td>
</tr>
<tr>
<td>19b Ph</td>
<td>[Rh₂{(S)-pttl}₄]</td>
<td>20b, 66</td>
<td>89⁴</td>
</tr>
<tr>
<td>19c (E)-CH=CHMe</td>
<td>[Rh₂{(S)-nttl}₄]</td>
<td>22, 77</td>
<td>67³</td>
</tr>
<tr>
<td>19c (E)-CH=CHMe</td>
<td>[Rh₂{(S)-pttl}₄]</td>
<td>22, 81</td>
<td>60⁴</td>
</tr>
</tbody>
</table>

a At 0 °C.
b At –78 °C.
c 1R,5S.
d 1S,5R,6S.
e 3aR,6R.

---

**Scheme 3**
the grounds of its CD in comparison to that of 24. The results indicate an inversion of the sense of absolute configuration between 20a as opposed to that of 20b and 20c. Precedents for such inversions upon change of substituents have been reported, however, for other intramolecular cyclopropanations of diazoacetates.16,17

A Formal Cycloaddition of 2,3-Dihydrofuran (25) via Cyclopropanation with Methyl (Silyloxyvinyl)diazoacetate (13)18

Diazo compounds, when exposed to transition-metal catalysts react with olefins usually via cyclopropanation. However, some oxocarbenes, when exposed to polar or polarizable olefins, undergo dipolar cycloadditions. For example, methyl diazoacetoacetate (2b), in the presence of [Rh₂{(S)-nttl}₄], reacts with 2,3-dihydrofuran (25) to afford the cycloadduct 26 in 30% yield and 33% ee (Scheme 4). The result is as unsatisfactory as the cyclopropanation of styrene with 2b mentioned above. However, if 2b is replaced by the vinyl diazoacetate 13, the cyclopropane 27 may be obtained with high enantioselectivity and yield. Treatment of the cyclopropane 27 with TBAF affords the formal cycloadduct 26.13

The cyclopropanation of 2,3-dihydrofuran (25) with 13 in the presence of [Rh₂{(S)-nttl}₄] afforded 27 as a single diastereoisomer (Scheme 4). The enantiomers of 27 were not separable; however, upon treatment with TBAF the silyloxy group of 27 was cleaved off, and the resulting ketone 28 underwent spontaneous ring-opening to 29 and recyclication to afford 26, on which the enantioselectivity could be determined by GC. In general, 27 was not isolated, and the yields reported in Table 4 refer to the two-step sequence. The yield for transformation of isolated 27 to 26 was in the order of 80%. Other catalysts were examined, but led to lower selectivities, except [Rh₂{(S)-pttl}₄]. The analogous reaction of 3,4-dihydro-2H-pyran (30) yielded the corresponding adduct 31 in 79% yield and 95% ee in the presence of [Rh₂{(S)-pttl}₄], as determined on 34 after treatment with TBAF (Scheme 4, Table 4). In view of these satisfactory results, no extensive screening with other catalysts was carried out. A secondary product 32 resulting from direct cycloaddition of 13 to 30 was also isolated in ca. 10% yield, but the enantioselectivity of the secondary process was not investigated.

Scheme 4
The racemic cyclopropane 31 was reduced with LiAlH₄ to afford the corresponding alcohol, which was derivatized with 3,5-dinitrobenzoyl chloride to afford 33. The structure of 33 was unambiguously confirmed by X-ray structure analysis. Unfortunately, no suitable crystals could be obtained from enantiopure derivatives from any compound in this series, and the absolute configuration of the products could not be established.

Cycloadditions with Dioxocarbenes

If the transition-metal-catalyzed diazo decomposition of diazo esters carrying a second carbonyl substituent is carried out in the presence of polar olefins, products of formal [2+3] dipolar cycloadditions may be formed. This is typically the case with ethyl diazoacetate (2d)¹⁹ and 2-diazodimedone (3)²⁰ but also with ethyl diazopyruvate (4).²¹ There is evidence that some of these cycloadditions are concerted; however, the occurrence of two-step additions involving intermediate cyclopropanes or dipolar species may not be definitely ruled out.

Cycloaddition of 2-Diazo-5,5-dimethylcyclohexane-1,3-dione (3a) to 2,3-Dihydrofuran (25)

2-Diazodimedone (3a) undergoes cycloaddition to 2,3-dihydrofuran (25) upon diazo decomposition to afford the adduct 36 (Scheme 5). Contrary to previous claims in the literature,²² these cycloadditions are not enantioselective when catalyzed by Rh(II).²³ In light of our observations with diazo acetooacetate presented above, we tried to circumvent the problem by preparing the silyl enol derivative 37 of diazodimedone; however, we were unable to isolate the desired product. Subsequently, we turned our attention to Ru catalysts. Recently, Mezzetti has reported highly diastereoid and enantioselective cyclopropanations of styrene with Ru catalysts. These cyclopropanations have exceptionally high (negative) ρ-values of −2.3.²⁴ By extending the reasoning of Davies mentioned above, we hypothesized that the Ru-catalyzed cycloadditions might exhibit higher enantioselectivities than the Rh-catalyzed reactions.

Scheme 5

![Scheme 5](image_url)

Table 4  Cyclopropanation–Rearrangement of 2,3-Dihydrofuran (25) and 3,4-Dihydro-2H-pyran (30) with 13

<table>
<thead>
<tr>
<th>Olefin Catalyst</th>
<th>Solvent</th>
<th>Product, ee, yield (%)</th>
<th>33 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>25</td>
<td>26, 44</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>CH₂Cl₂</td>
<td>26, 63</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>pentane</td>
<td>26, 58</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>PhF</td>
<td>26, 77</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>toluene,</td>
<td>26, 68</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>toluene,</td>
<td>26, 75</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-ptpa)₄]</td>
<td>toluene,</td>
<td>26, 95</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-ptpa)₄]</td>
<td>toluene,</td>
<td>26, 59</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-dosp)₄]</td>
<td>toluene,</td>
<td>26, 50</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-bn)₄]</td>
<td>toluene,</td>
<td>26, 35</td>
</tr>
<tr>
<td>25</td>
<td>[Rh₂((5)-mepy)₄]</td>
<td>toluene,</td>
<td>26, 43</td>
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<tr>
<td>30</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>toluene,</td>
<td>31, 78</td>
</tr>
<tr>
<td>30</td>
<td>[Rh₂((5)-nttl)₄]</td>
<td>toluene,</td>
<td>31, 79</td>
</tr>
<tr>
<td>30</td>
<td>[Rh₂((5)-dosp)₄]</td>
<td>toluene,</td>
<td>31, 68</td>
</tr>
<tr>
<td>30</td>
<td>[Rh₂((5)-dosp)₄]</td>
<td>toluene,</td>
<td>not detected</td>
</tr>
</tbody>
</table>

a Conditions: At 0 °C, 13 (0.3 mmol) was reacts with 25 or 30 (10–15 equiv), respectively, in the appropriate solvent (3.0 mL), and catalyst (3 %).
b Determined based on 32 by GC.

Our expectations were only partially satisfied.²⁵ Under optimized conditions the Ru-catalyzed cycloaddition of 2-diazodimedone (3a) to 25 in the presence of the pybox ligand 35 (10 mol%) produced the adduct 36 in only 40% yield although with 56% ee. With 5 mol% of catalyst, the yield was 22% (in CH₂Cl₂). The yield increased to 70% when the reaction time was increased to 72 hours, and to 76% when the reaction was carried out at 45 °C with 5 mol% of catalyst. In this latter case, the ee decreased slightly to 52%. A large selection of Ru catalysts was screened, but the enantioselectivity of the reaction could not be improved. In the hope of speeding up the reaction, the diazo precursor 3a was replaced by the corresponding phenylidonium ylide 3c. However, the results with ylide
Cycloaddition of Ethyl Diazopyruvate (38) to 2,3-Dihydrofuran (25)²⁵

The diazo decomposition of ethyl diazopyruvate (38) in the presence Rh(II) carboxylate catalysts afforded good yields of adduct 39, but the reactions were not enantioselective (Scheme 6, Table 5). With Ru–pybox catalysts, the cycloadditions of 38 contrary to those of 3a proceeded conveniently at room temperature, although the Ru-catalyzed reactions afforded lower yields of 39 than the Rh(II)-catalyzed ones.

The catalysts were prepared according to published procedures: [Rh₂{(S)-nttl}₄]¹⁴₁⁷, [Rh₂{(R)-ntv}₄]¹⁴₁⁷, [Rh₂{(S)-4-X-nttl}₄]²⁶, [Rh₂{(S)-dosp}₄]²⁶, [Rh₂{(S)-tbp}₄]²⁷, [Rh₂{(S)-ptpa}₄]²⁸, [Rh₂{(S)-pitt}₄]²⁹, [Rh₂{(S)-mepy}₄]³⁰, [Rh₂{(S)-bnp}₄]³¹, [RuCl₂(p-cymene)]²³.

One-Pot Cyclopropanation of Olefins with Dimethyl Malonate; General Procedure

Dimethyl malonate (7: 1.32 g, 0.01 mol, 1 equiv) was added to a mixture of iodosylbenzene (1.4 equiv), olefin 6 (10 equiv), MgO (2.3 equiv), rhodium(II) catalyst (5 mol%) and molecular sieves 4 Å (250 mg) in CH₂Cl₂ (10 mL). The mixture was stirred under argon for 24 h. Samples (100 μL) were taken after several time intervals. The samples were filtered using a syringe filter holder (0.2 μm pore size) and the organic layer was diluted with CH₂Cl₂ (100 μL) and analyzed by GC. The reaction progress was monitored qualitatively by TLC using heptane–EtOAc (5:1) as eluent. An aliquot of the supernatant was used for GC analysis. When maximum conversion was reached, the reaction was terminated by filtration through Celite. The Celite pad was washed with CH₂Cl₂ (2 x). Evaporation of the combined filtrates under reduced pressure followed by chromatography on silica gel with heptane–EtOAc (5:1) as eluent afforded the desired cyclopropane derivatives 10.

Cyclopropanation of Styrene with Methyl (Trisopropylsilyl-oxovinyl)diaoaoacete (13); (1R,2S)-1-[Tris(isopropylsilyloxyvinyl)-2-phenylcyclopropanecarboxylate (14a)

The catalyst [Rh₂{(S)-nttl}₄] (11.6 mg, 0.008 mmol) was activated by heating in vacuo, and dissolved in toluene (3.0 mL). After addition of styrene (6a: 730 mg, 7.0 mmol) the mixture was cooled to 0 °C, and 13 (208 mg, 0.70 mmol) in toluene (2.0 mL) was added dropwise. After the addition, stirring was continued for 1 h. The solvent was evaporated and the residue was purified by flash chromatography (SiO₂, Et₂O–pentane, 5:95) to afford 14a (194 mg, 77%) as a colorless solid. For data, see ref. 7.

Intramolecular Cyclopropanation of Allyl 2-Diazo-3-silyloxybut-3-ene (19a); (1R,5S)-1-[1,3-Tris(isopropylsilyloxyvinyl)-3-oxabicyclo[3.2.0]hexan-2-one (20a); Typical Procedure

[Rh₂{(S)-nttl}₄] (13.9 mg, 0.01 mmol) was activated by heating in vacuo, and dissolved in toluene and cooled to 0 °C. The diazoacate 19a (152.4 mg, 0.47 mmol) in toluene (1.0 mL) was added dropwise. After stirring for 1 h, the solvent was evaporated and the residual...
idue was purified by flash chromatography (SiO$_2$, Et$_2$O-pentane 15:85) to afford **20a** as a colorless oil in 81% yield. For data, see ref. 15.

**Cyclopropanation–Rearrangement of 2,3-Dihydrofuran (25)**

with Methyl (Triisopropylsilyloxyvinyldiazoacetate (13); Methyl cis-2-Methyl-3a,4,5,6a-tetrahydrofuran-2,3-b[furan-3-carboxylate (26)

The catalyst (1.0 mol%) was activated by heating in vacuo and dissolved in toluene (2.0 mL). 2,3-Dihydrofuran (25, 10 equiv) was added and the mixture was cooled to 0 °C. The diazoacetate 13 (0.30 mmol) in toluene (1.5 mL) was added dropwise with stirring. After the addition, stirring was continued for 1 h. The solvent was evaporated and the residue was dissolved in Et$_2$O (5.0 mL) and the resulting suspension was stirred until complete consumption of the starting material (TLC). The mixture was concentrated, and the residue was purified by flash chromatography (SiO$_2$, Et$_2$O–pentane 16:84 to afford 26 (77%) as a colorless oil. For data, see ref. 18.

**Cycloaddition of Ethyl 2-Diazopyruvate (38) to 2,3-Dihydrofuran (25); Ethyl 4,5-Dihydro-3a-furo-2,3-b[furan-2-carboxylic acid (39)

(S),S)-2,6-Bis(4-isopropyl-2-oxazolin-2-yl)pyridine (86 mg, 0.294 mmol) was added to a solution of [RuCl$_2$(py-cymene)]$_2$ (58 mg, 0.095 mmol) in CH$_2$Cl$_2$. The dark-red mixture was stirred at r.t. for 1 h under argon. The solvent was removed under reduced pressure. 2,3-Dihydrofuran (25, 1.4 mL) and a solution of ethyl diazopyruvate (38; 100 mg, 0.95 mmol) in toluene (3.0 mL) was added. The resulting suspension was stirred until complete consumption of starting material (TLC). The mixture was concentrated, and the residue was purified by column chromatography on silica gel using EtOAc–pentane (60:40) as eluent to afford 39 as pale-yellow solid.

**Acknowledgment**

This work was supported by the Swiss National Science Foundation (projects No. 20-52581.97 and 2007-048156). The support and sponsorship conceded by COST Action D24 (‘Sustainable Chemical Processes: Stereoselective Transition Metal-Catalysed Reactions’) are kindly acknowledged.

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