Regioselective and Enantiospecific Synthesis of Dioxepines by (Cyclopentadienyl)ruthenium-Catalyzed Condensations of Diazocarbonyls and Oxetanes

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Abstract: 1,4-Dioxepines result from the decomposition of α-diazo-β-keto esters in the presence of oxetanes using the catalytic combination of the (cyclopentadienyl)ruthenium complex [CpRu(CH3CN)3][BARF] and 1,10-phenanthroline. The regioselective [4+3] insertions follow an S_N1-like mechanism and occur yet enantiospecifically (es 74%). The retention of configuration was ascertained by vibrational circular dichroism (VCD) and solid state analyses. Furans, products of [4+1] insertions, are only observed as traces in the above protocol. To promote their formation under CpRu catalysis, it is necessary to use a two-step process with γ-halogenated alcohols as substrates.

Keywords: diazo compounds; insertion; metal carbenes; oxetanes; oxonium ylides; retention of configuration

Seven- to eleven-membered cycles, also called medium-sized rings, are important building blocks, being present in a large variety of biologically relevant natural and medicinal products. Due to strain and entropy factors, their synthesis is often challenging but it can be approached with confidence through cycloaddition, ring-closing metathesis, coupling or ring expansion reactions among others. In the particular context of ring-expansions, the use of reactive substrates such as readily accessible oxetanes can be advantageous. In fact, the high nucleophilicity of oxygen lone pairs and the important ring strain (≈25 kcal mol⁻¹) permit the facile formation of reactive oxonium ylide intermediates that decompose spontaneously into higher ring systems regio- and stereoselectively. For instance, under Cu catalysis or photochemical conditions, diazo reagents react with oxetanes in [4+1] processes to form substituted furans (Scheme 1a, [1,2]-shift mechanism). On the contrary, under Rh(II) or Pd(II) catalysis, decompositions of α-diazo-carbonyls in the presence of oxetanes (solvent) afford 15-membered macrocycles by [3+4+4+4] condensation (Scheme 1b). Recently, it has been shown that combinations of 1,10-phenanthroline (phen) and [CpRu(CH3CN)3][X] (X = PF6 1a or X = BARF, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate 1b) efficiently catalyze the decomposition of α-diazo-β-keto esters and promote selective 1,3-C–H insertions into THF and condensation reactions with ketones, lactones and cyclic carbonates. With oxiranes (epoxides), [3+3] insertions lead to the formation of a large variety of 1,4-dioxene moieties. Herein, in a new development, condensations of oxetanes with α-diazo-β-keto esters under Rh(II) and Pd(II) catalysis were attempted with the aim of accessing higher rings (Scheme 1d). However, the use of [CpRu(CH3CN)3][BARF] 1b as catalyst and [R3ArN=O][BARF] 2 as substrate instead of α-diazo-β-keto esters under Rh(II) or Pd(II) catalysis led to 1,4-dioxene formation (Scheme 1c). For this purpose, we have employed C–H arylation and C–H oxygenation reactions using the [CpRu(CH3CN)3][BARF] 1b catalyst and [R3ArN=O][BARF] 2 as substrates under Rh(II) or Pd(II) catalysis, respectively. We have found that this approach provides a straightforward route to 1,4-dioxene formation, with regio- and stereoselectivity. The reaction proceeds through a multi-step process involving the formation of a reactive oxonium ylide intermediate, its decomposition into higher ring systems and the subsequent condensation reactions with ketones, lactones and cyclic carbonates.

Scheme 1. Oxonium ylide formation by decomposition of diazo reagents in the presence of oxetanes and subsequent reactivity (a, b or c).
tanes 2 and α-diazo-β-keto esters 3 under CpRu-catalysis are reported affording 1,4-dioxepines 4 (Scheme 1c). To the best of our knowledge, it is the first report of 7-membered heterocycle formation in this type of reaction. Of interest, the 1,4-dioxepines are obtained as single regioisomers via $S_N$1-like mechanisms that proceed nevertheless with a certain level of enantiospecificity (es 74%); the retention of configuration being ascertained by vibrational circular dichroism (VCD) analysis.

As just mentioned, efficient decomposition of diazo-carbonyls can be provided by the catalytic combination of [CpRu(CH$_3$CN)$_3$] salts 1 and diimine ligands. In many instances, in the presence of carbonyl groups and cyclic ethers, rather unexpected reactivities were reported.$^{[12-14]}$ These results led us to consider the reactivity of other Lewis bases with the catalytic combination, and oxetanes in particular. The first experiments were achieved by dissolving 2-naphthaleneyloxetane 2a (1.0 equiv.) in a CH$_2$Cl$_2$ solution of complex 1b and phen (2.5 mol% each). In practice, diazoacetatoacetate 3A (2.0 equiv.) was added in one portion and the mixture was warmed up to 60°C. From the beginning, dinitrogen release could be observed and the reaction mixture was stirred until full conversion of oxetane 2a (16 hours, TLC monitoring). $^1$H NMR spectroscopic analysis of the crude reaction mixture led to the identification of ring-expanded 7-membered ring 4aA in low yield (18% NMR).$^{[15]}$ In view of the importance of 7-membered heterocycles in synthesis and medical chemistry, it was decided to study the reaction further and improve the reactivity. However, despite many attempts (see the Supporting Information), the optimization of the reaction was rather difficult and only a moderate increase in yield was achieved. Eventually with a milder procedure, decreasing the temperature down to 30°C and using 5 mol% of catalyst led to full conversion of starting 2a in 16 hours and 4aA was obtained with a yield of 35% (Table 1, entry 1). The structure of 4aA was confirmed by X-ray diffraction analysis (Table 1, Supporting Information).$^{[16]}$ With these conditions in hand, various diazocarboxyls were reacted. Using diazo reagents with longer alkyl ester chains, such as ethyl 3B and benzyl 3C, slightly higher yields were obtained in the presence of oxetane 2a (entries 2 and 3). Not surprisingly, the sterically hindered adamantyl group was found to have a negative effect on the formation of 4aD as an oxetane conversion of only 50% was observed after extended reaction time (3 days, entry 4). $p$-Chlorophenyl substrate 3E was tolerated as product 4aE was obtained with a similar yield to that of the methyl derivative 4aA (entry 5). With tosyl or mesyl groups instead of ester moieties, formation of 1,4-dioxepines 4aF and 4aG was achieved in 39% and 38%, respectively (entries 6 and 7). Furthermore, introduction of an α-keto ester group in place of the acetyl moiety led to diester dioxepine 4aH in 19% yield only (entry 8). The reason for the lower reactivity could be the lesser nucleophilicity of the enolate intermediate (vide infra, Scheme 2, species D with R$^2$ = CO$_2$Et). Alternatively, 4aH was found to be particularly sensitive to acidic conditions and the lower yield

![Table 1. Diazocarbonyl reactivity.][a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>2a (1 equiv.)</th>
<th>3A–3I (2 equiv.)</th>
<th>[Ru] (5 mol%)</th>
<th>phen (5 mol%)</th>
<th>CH$_2$Cl$_2$</th>
<th>30 °C, 16 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b (5 mol%), phen (5 mol%), CH$_2$Cl$_2$, 30°C, 16 h unless otherwise noted, c=0.5 M; conversions (conv.) determined by $^1$H NMR spectroscopy. ORTEP view of the crystal structure of 4aA. Thermal ellipsoids are drawn at 50% probability, Ad=1-adamantyl; Ts=$p$-toluenesulfonyl and Ms=methanesulfonyl.</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4aB yield: 39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>4aC yield: 40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4aD yield: 22% (conv.: 50%, 3 d)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4aE yield: 36%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4aF yield: 39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4aG yield: 38%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4aH yield: 19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4aI yield: 35%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1b (5 mol%), phen (5 mol%), CH$_2$Cl$_2$, 30°C, 16 h unless otherwise noted, c=0.5 M; conversions (conv.) determined by $^1$H NMR spectroscopy. ORTEP view of the crystal structure of 4aA. Thermal ellipsoids are drawn at 50% probability, Ad=1-adamantyl; Ts=$p$-toluenesulfonyl and Ms=methanesulfonyl.
could be the result of a degradation during purification (silica gel chromatography). Finally, trisubstituted enol ether 4aI was obtained in 35% yield using an aldehyde-containing diazo ester reagent (entry 9).

After this first screen of diazo reactivity, the reaction was performed with various oxetanes (Table 2).[^1] 1-Naphthalenyl substrate 2b afforded the corresponding 7-membered ring 4bB with a lower yield than 4aB, due probably to the increased steric hindrance (Table 2, entry 1). A higher yield of 4cB was however obtained with 1-phenyloxetane (entry 2, yield 54%, Table 2).[^1]

Globally, this increased reactivity was confirmed with phenyl substituents carrying electron-withdrawing (F, Cl) or electron-donating (Me) groups at the para position of the aromatic ring (4dB–4fB, entries 3 to 5, 55–61%); the reactivity being lower only in the presence of a bulkier mesityl group (4gB, entry 6, 41%). Finally, p-tolyloxetane 2f was reacted with three other α-diazo-β-keto esters. While similar results were obtained with isobutyl and 2-methoxyethyl chains (4fJ–4fK, entries 7 and 8, 52% and 53% respectively), a slightly lower yield was observed with the trichloroethyl carbonate (Troc) ester (4fL, entry 9, 40%).

Additionally and of importance for the mechanistic discussion, the enantiomeric purity of the reaction was examined. Enantioenriched oxetane (R)-2c (ee > 99%) was synthesized under reported conditions.[^9]

Treatment under the optimized conditions led to 1,4-dioxepine (−)-4cB with exactly the same yield [Eq. (1)]. Chiral stationary phase HPLC analysis indicated an enantiomeric ratio of 87:13 for 4cB and hence a chirality transfer (enantiospecificity) of 74%.

Interestingly, in terms of stereospecific transformations, only Sn2 ring expansions of oxetanes have been reported.[^4,5] Care was thus taken to determine the absolute configuration of product (−)-4cB. It was established by vibrational circular dichroism (VCD). A comparison between measured VCD spectra for both (−)-4cB and (−)-4cB obtained enantiomerically pure by semi-preparative CSP HPLC separation of (±)-4cB with the theoretical spectrum of the most stable conformers (Boltzmann distribution) of (R)-4cB was performed (Figure 1). A good agreement was achieved between experimental and theoretical spectra of (−) and (R)-configured 4cB. This finding is in agreement with what was observed in the X-ray crystallographic study of (−)-4cB (see the Supporting Information). Due to the lack of heavy atoms in the structure, the Flack parameter could not be determined with good precision but its value was found to be around zero [x = −0.13(16)]. These results clearly indicate that the formation of 4cB occurs with a global retention of configuration.

At this stage, a mechanistic rationale can be proposed (Scheme 2). First, ruthenium salt 1b reacts with phen to generate complex [CpRu(phen)(CH\textsubscript{3}CN)][BAR\textsubscript{5}]. Then, upon dissociation of the acetonitrile ligand, catalytically active 16-electron species A is formed. After nucleophilic attack of diazo reagents 3 onto A and dinitrogen extrusion, metal carbenes of type B are generated. Intermediates B behave as electrophilic Fischer carbenes and nucleophilic attacks of Lewis basic oxetanes yield metal-bound oxonium ylide intermediates C. Due to ring strain and the electrophilic activation of the aromatic rings, regioselec-

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**Table 2. Oxetane reactivity.**[^a]

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>2g</td>
<td>[Ru] (5 mol%), phen (5 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 30 °C, 16 h</td>
<td>32%</td>
</tr>
<tr>
<td>3B</td>
<td>3J–3L</td>
<td>(2 equiv.)</td>
<td>54%</td>
</tr>
<tr>
<td>3B</td>
<td>3J–3L</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}, 30 °C, 16 h</td>
<td>55%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>56%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>55%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>41%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>52%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>4fB</td>
<td>4gB</td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>

[^a] Reaction conditions: 1b (5 mol%), phen (5 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 30 °C, c = 0.5 M.
tive C–O bond cleavage occurs to form stabilized carboxcatic intermediates D. The neighboring carbonyl groups then trap the carbocations leading to fast intramolecular 7-membered ring formation (D→E). After decomplexation, catalyst A and the 1,4-dioxepines are released. Importantly, this mechanistic rationale explains not only the global S_N_1-like regioselectivity but also the observed (partial) retention of configuration with substrate (R)-4cB. In fact, the proximity between the carbonyl groups and the secondary carboxcatic center in D ensures rapid 7-endo-trig cyclization. This avoids, to a large extent, the scrambling of the stereotopic faces of carbenium ions D (through internal C–C rotations) and the racemization.

Also of mechanistic importance, acid-sensitive furan 5c could be isolated from the reaction of oxetane 2c with 3B (Scheme 3). In fact, careful analysis revealed a proportion of 5–10% of 5c in crude mixtures (GC-FID estimation). The formation of 5c can be explained by a second route starting from intermediates C or D (Scheme 3). At that stage, direct C-alkylation gives rise to furan 5c, of a structure similar to that described by Nozaki and Noyori. Moreover, 5c is isolated as a single diastereomer, an observation that tends to indicate a highly stereoselective process as described in the literature. The preferred formation of 4cB over 5c can be explained by Baldwin’s rules since 7-endo-trig cyclizations are favored over 5-endo pathways.

Finally, Bull and co-workers have described recently the formation of 1,4-dioxenes in two steps using β-halogeno alcohols as substrates. In a first step, CpRu-catalyzed O–H insertions of α-diazo-β-keto esters occur, followed by intramolecular cyclizations under basic conditions. Using this protocol, only O-alkylations of ketoenolate intermediates are observed leading to a large variety of dioxenes. In view of the efficiency of the method, care was taken to apply it for the synthesis of 1,4-dioxepines. Reactions under CpRu catalysis of alcohols 6c and 6h with 3B afforded halogenated keto esters 7c and 7h in good yields, 90% and 79% respectively (Scheme 4). These compounds were then treated with NaH (1.2 equiv.) in DMF. However, instead of forming 1,4-dioxepine products, reactions afforded oxolanes 5c and 5h exclusively (62% and 70% yields). Clearly, the ketoenolate intermediates undergo C-alkylation preferentially to form the corresponding furans. According to Baldwin’s rules, both 5-exo and 7-exo-tet cyclizations are fa-
Scheme 4. 5- vs. 7-membered ring cyclizations.

In conclusion, the combination of [CpRu(CH$_3$CN)$_3$]$_2$BAr$_6$ and 1,10-phenanthroline leads to a new reactivity between α-aryloketanes and carbones derived from α-diazo-κ-keto esters. 1,4-Dioxepines are obtained in moderate yields but with a good enantiomeric purity in an original S$_8$1-like transformation, as determined by VCD and X-ray diffraction analyses. Baldwin’s rules for the ring closure can be applied to explain the preferential formation of dioxepines 4 vs. furan 5.

Experimental Section

General Procedure

In a 2-mL screw-cap vial equipped with a magnetic stirring bar, 1,10-phenanthroline (3 mg, 16 μmol, 5 mol%) and [CpRu(CH$_3$CN)$_3$]$_2$BAr$_6$ (18 mg, 16 μmol, 5 mol%) were dissolved in 0.60 mL of dry dichloromethane. The vial was flushed with nitrogen and capped. The resulting deep red solution was stirred for 10 minutes at 25°C before the addition of oxetane 2 (0.32 mmol, 1 equiv.) and the desired diazo derivative 3 (0.64 mmol, 2 equiv.). The solution was stirred at 30°C until full conversion (H NMR monitoring). The crude mixture was purified by column chromatography (pentane/Et$_2$O/SiO$_2$) to afford 1,4-dioxepine 4.

Acknowledgements

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References


[15] ‘H NMR monitoring of the crude reaction mixture indicates products of degradation and of polymerization of 2. Their isolation was not possible.

[16] CCDC 1551193 and CCDC 1551194 contain the supplementary crystallographic data for this paper, products 4aA and (+)-4cB, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] Alkyl-substituted oxetanes were unreactive under the optimized reaction conditions.

[18] The reaction was scalable up to a 1 g scale (8 mmol) (see the Supporting Information).


[20] Overlapping ‘H NMR signals of 1,4-dioxepine 4 and furan 5 rendered the spectroscopic analysis difficult for a quantitative study.

[21] A selective and complete decomposition of the second diastereomer upon purification might be an alternative explanation.