## **Domino Reactions**

## **Rhodium-Catalyzed Domino Enantioselective Synthesis of Bicyclo-**[2.2.2]lactones\*\*

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Increasing focus is placed upon achieving efficiency in processes and syntheses in organic chemistry. The combination of multiple reactions into domino sequences is an excellent way to achieve efficiency, with several operations proceeding in concert without recourse to expensive and wasteful purification at each intermediate stage.<sup>[1]</sup> The rhodium-catalyzed asymmetric ring-opening (ARO) reaction of strained oxabicyclic alkenes using heteroatom nucleophiles has been well-studied and been demonstrated to be a highly efficient enantioselective process (e.g.  $1\rightarrow 2$ , Scheme 1).<sup>[2-4]</sup>





**Scheme 1.** An overview of the nucleophilic asymmetric ring-opening reaction.  $(R, S_p)$ -Josiphos = (R)-(-)-1- $[(S_p)$ -2-(diphenylphosphino)-ferrocenyl]-ethyldi-*tert*-butylphosphine.

However, rhodium is also capable of many other catalytic transformations owing to its reactivity with  $\pi$  bonds, alcohols, aldehydes, and boronic acids.<sup>[5]</sup> Herein, we report a novel domino process in which rhodium is demonstrated to perform three distinct roles: ARO, allylic alcohol isomerization, and oxidation ( $3 \rightarrow 5$ , Scheme 1).

The ergoline alkaloids are often described as the most potent family of natural products.<sup>[6]</sup> The core motif of these

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alkaloids is an aminotetralin core (Scheme 1; dashed box), which we reasoned could be created efficiently with ARO chemistry. Previously, the ARO reaction of bridgehead unsubstituted oxabicyclic alkenes has been demonstrated to be effective for a wide range of nucleophiles, to give products in excellent yield and enantioselectivity.<sup>[2-4]</sup> The incorporation of one symmetry-breaking substituent at the bridgehead has been demonstrated to be tolerated, resulting in regiodivergent resolution to two products, each in approximately 50% yield. Recognizing that the aminotetralin core of the ergoline natural product family is highly substituted, we sought a more-functionalized building block and selected the doubly bridgehead substituted oxabicyclic alkene **3**. This substrate was readily available in two steps from furfuryl alcohol.<sup>[7]</sup>

The increased steric demand of the two hydroxymethyl groups coupled with their inductive electron-withdrawing nature meant that many of the catalysts previously employed in the ARO reaction<sup>[3]</sup> failed to induce ring opening (Table 1;



[a] Oxabicyclic alkene diol (0.2 mmol, 1 equiv), amine nucleophile (1.1 equiv). [b] Yield of the isolated product after column chromatography on silica gel. [c] The *ee* value was determined by HPLC using a chiral stationary phase. [d] 20 mol%. [e] 1 equiv. [f] A comparable yield of **4a** was obtained with 1 equiv of water. [g] Molecular sieves (4 Å) were used in catalyst preparation. cod = 1,5-cyclooctadiene, n.d. = not determined, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.

0.1 м, 60°С, 1 h

0.3 м, 60°C, 18 h

\_[f]

\_[g]

3

4

entries 1 and 2). Conversely, the cationic RhOTf/Josiphos system was able to promote the desired transformation in only 1 hour. At low concentrations, the reaction gave only the product resulting from the ARO reaction (**4a**) with good yield and excellent enantioselectivity (Table 1; entry 3). However, upon an increase in the reaction concentration, an extension of the reaction time, and with the exclusion of moisture, we observed the clean formation of a new compound whose IR and <sup>13</sup>C NMR spectra indicated the presence of a lactone

65 (98)

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(Table 1, entry 4). Full analysis of the spectral data revealed the product to be the [2.2.2]bicyclic compound **5a**.

To investigate this process, the reaction between a range of secondary amine nucleophiles and a selection of substituted oxabicyclic alkenes was explored. The reaction gave the lactone products **5** with uniformly high levels of stereoselectivity for all the amines that were investigated, including those with hydrocarbon substituents (**5a–f**, Table 2) as well as amines bearing ether, acetal and ester functionalities (**5g–i**, Table 2). Although chiral amine nucleophiles such as (*S*)-*N*methyl-1-phenylethanamine **j** have been demonstrated to induce selectivity in many organic transformations,<sup>[8]</sup> the powerful rhodium catalyst/ligand system was unaffected by

*Table 2:* Domino formation of bicycle[2.2.2]lactones with dialkylamine nucleophiles.

Entry <sup>[a]</sup>	Nucleophile	Product	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	HN _ Ph a	HO , , , , , , , , , , , , ,	65 <sup>[d]</sup>	98 <sup>[d]</sup>
2	Ph HN_Ph <b>b</b>	HO O 5b	58	>98
3	HN c		64	>98
4	HN	HO O 5d	64	>98
5	e	HO O 5e	62	97
6	HN f		65	>98
7	HN g	HO N O 5g	62	> 98
8	h h		78	>98

#### Table 2: (Continued)



[a] Reagents and reaction conditions: oxabicyclic alkene diol (ca. 0.2 mmol, 1 equiv), amine nucleophile (1.1 equiv), [Rh(cod)<sub>2</sub>OTf] (5 mol%), ( $R,S_p$ )-Josiphos (6 mol%), THF (0.3 M), 60 °C, 16–18 h. [b] Yield of the isolated product after flash column chromatography on silica gel. [c] The *ee* value was determined by HPLC using a chiral stationary phase and the d.r. determined by <sup>1</sup>H NMR analysis of the reaction mixture. [d] Approximately 0.6 mmol of oxabicyclic alcohol was used and the yield is an average over three experiments. [e] ( $S,R_p$ )-Josiphos (6 mol%) was used as the ligand.

the stereochemistry of the amine nucleophile, and by choosing an appropriate ligand we were able to access each of the diastereomeric products 5j and 7j with exquisite selectivity. The use of a different oxabicyclic alkene substrate with an extended aromatic backbone was well-tolerated and the bicyclic lactone product 9j was formed in > 20:1 d.r. (Scheme 2).



*Scheme 2.* Domino reaction with substituted benzo-oxabicyclic alkene substrates.

Aniline nucleophiles have been previously demonstrated to be competent nucleophiles in the ARO reaction, and often give more favorable results than alkylamines.<sup>[3c]</sup> However, applying the reaction conditions used for the alkylamines to the aniline nucleophiles (i.e. *N*-methylaniline) led to exclusive formation of the ARO product (**4k**) in high yield and enantioselectivity (Scheme 3). There are substantial differences in the basicity of an aniline nitrogen atom versus an alkylamine nitrogen atom, therefore triethylamine (1.1 equiv) was added to the reaction mixture and we were pleased to obtain the lactone product (**5k**) with comparable yield and

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**Scheme 3.** Domino formation of bicycle[2.2.2]lactones with aniline nucleophiles. Reagents and reaction conditions: oxabicyclic alkene diol (ca. 0.2 mmol; 1 equiv), amine nucleophile (1.1 equiv), triethylamine (1.1 equiv), [Rh(cod)<sub>2</sub>OTf] (5 mol%), ( $R,S_p$ )-Josiphos (6 mol%), THF (0.3 M), 60 °C, 16–18 h.

selectivity to those achieved with dialkylamines. Again the reaction proved general for several different anilines (5k-n) and furthermore, the crystalline products 5k and 5n allowed us to unequivocally confirm the bicyclic lactone structure and absolute stereochemistry.<sup>[9]</sup>

When considering the mechanism for the formation of these unexpected and interesting products, it was reasoned that the ARO reaction would be the first step in the sequence (Scheme 4, A), since under milder reaction conditions it occurred rapidly and efficiently (Table 1, entry 3). The resulting intermediate **4** contains an alkene that could be isomerized to the corresponding aldehyde **11'** (Scheme 4, B).<sup>[10]</sup> The aldehyde **(11')** thus formed would be in close proximity<sup>[11]</sup> to the tertiary alcohol and lead to the formation of a hemiacetal,<sup>[12]</sup> which could be oxidized under the optimized reaction conditions to give the observed product **5** (Scheme 4; C).<sup>[13,14]</sup>

To study the reaction mechanism, the intermediate 4a, which was formed after the first step of the proposed threestep sequence, was subjected to the optimized reaction



Scheme 4. Proposed mechanism for the lactone formation.

conditions (Scheme 5). The triol **4a** underwent an isomerization/oxidation domino sequence to give the lactone **5a**, however the addition of triethylamine was also required for



*Scheme 5.* Experiments to support the proposed domino mechanism for the lactone formation.

this transformation.<sup>[7]</sup> Most importantly, we prepared the deuterium-labelled substrate  $[D_4]$ -3 and this reacted to give the product  $[D_3]$ -5a, which is consistent with the proposed mechanism.

In summary, we have achieved the first intermolecular rhodium-catalyzed ARO reaction of doubly bridgehead substituted oxabicyclic alkenes. Furthermore, we discovered a domino reaction which affords bicyclo[2.2.2]lactone products in good yield and with excellent enantioselectivity. Our preliminary mechanistic investigations suggest that rhodium plays three distinct roles in the reaction. We are currently performing further experiments to fully elucidate the mechanism of the process and investigate the application of these novel intermediates to natural product synthesis. Furthermore, the lactone products themselves are of particular interest as bicyclic lactones can be found at the core of several bioactive natural products.<sup>[15]</sup>

### **Experimental Section**

Gemeral procedure: To a mixture of  $[Rh(cod)_2OTf]$  (55 mg, 0.12 mmol, 5 mol%),  $(R,S_p)$ -Josiphos (76 mg, 0.14 mmol, 6 mol%) and molecular sieves (4 Å) was added THF (3 cm<sup>3</sup>). The reaction vessel was flushed with Ar and stirred at ambient temperature for 10 min. The catalyst solution was added to a solution of **3** (480 mg, 2.4 mmol, 1.0 equiv) and *N*-benzylmethylamine (**a**; 313 mg, 2.6 mmol, 1.1 equiv) in THF (3.5 cm<sup>3</sup>). The reaction vessel was sealed and the contents heated to 60 °C for 16 h. The reaction mixture was allowed to reach ambient temperature and then transferred to a round-bottomed flask with ethyl acetate. The crude solution was concentrated and purified by flash column chromatography on silica gel (gradient from 10 to 50% ethyl acetate in pentane) to give **5a** (490 mg, 65%) as a pale yellow oil.

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