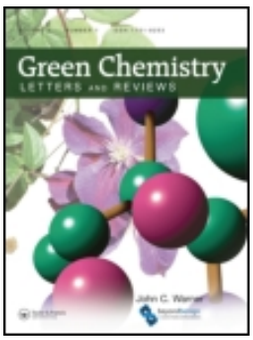

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## RESEARCH LETTER

# Intramolecular C–H insertion catalyzed by dirhodium(II) complexes using $CO_2$ as the reaction media

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In this work, the intramolecular C–H insertion of diazoacetamides catalyzed by dirhodium(II) complexes and using $CO_2$ as solvent is disclosed. The expected lactams were obtained in yields over 97%. The asymmetric intramolecular C–H insertion was also achieved and the β-lactam 14 was obtained in >97% yield and 65% *ee* using the chiral dirhodium(II) catalyst $Rh_2$(*S*-PTTL)$_4$. Finally, the dirhodium(II) complex $Rh_2(OAc)_4$ was used in two consecutive cycles in which complete conversion to the lactam was observed.

**Keywords:** diazoacetamides; C–H insertion; dirhodium(II); lactams; sc$CO_2$

## Introduction

The C–H insertion reaction of diazo compounds catalyzed by dirhodium(II) complexes has developed in to a very reliable methodology to form new C–C bonds from otherwise unreactive C–H bonds. As shown in Scheme 1, this reaction involves the generation of a metallocarbene that undergoes the C–H insertion forming the new C–C bond and at the same time that regenerates the catalyst (*1–8*).

From the sustainability point of view, the catalyzed C–H bond insertion starting from diazo compounds is an ideal process as it affords important C–C bonds generating nitrogen as the sole waste if only the C–H insertion step is considered. In order to further improve the sustainability of this methodology, it is important to introduce more benign reaction media as the reaction is typically carried out in organic solvents such as dichloromethane in order to avoid catalyst inhibition due to solvent coordination onto the complex axial positions (Scheme 1) (*1–8*). In addition to this, dirhodium(II) complexes are quite expensive and for that reason methodologies that enable the catalyst recycling are of pivotal importance(*9–20*). Over the years, we have been particularly interested on developing methods to perform the catalyst reutilization and on the study of new solvents to perform this reaction. In this field, we established ionic liquids as the reaction media in which the catalyst reutilization was achieved in six cycles, and we discovered that water could also be very efficiently used as a solvent allowing the catalyst reutilization ($Rh_2(OAc)_4$) in over 11 cycles (*21–25*). Despite the usefulness of these approaches, both required the product extraction using organic solvents and product purification. Taking this into consideration, we conceived that an ideal methodology would involve the reaction taking place in a solvent that affords the product in high yields and at the same time that enables the product/catalyst separation, leaving the complex ready for another reaction cycle. Considering the aforementioned requirements, we envisioned that supercritical $CO_2$ (*sc*$CO_2$) could be the solvent of choice for this process.

## Experimental

General procedure for the cyclization of diazoacetamide with dirhodium(II) complexes in $CO_2$: A 3.5-mL high-pressure cell was charged with diazoacetamide (0.173 mmol) and dirhodium(II) complex (1 mol%) and placed inside a constant temperature water bath. $CO_2$ was introduced into the cell by a screw injector pump, at a constant temperature of 30°C. The mixture was stirred with a magnetic stirrer for 24 hours under 30°C and 70 bar. After which, the system was depressurized and the product was filtered

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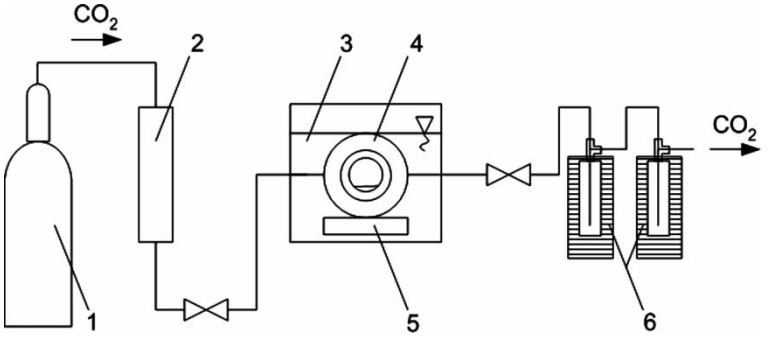



Figure 1. Schematic diagram of the apparatus for the cyclization of diazoacetamide with dirhodium(II) complexes in $CO_2$: 1, $CO_2$ supply; 2, screw injector pump; 3, constant temperature water bath; 4, high-pressure cell; 5, magnetic stirrer; 6, cold traps.

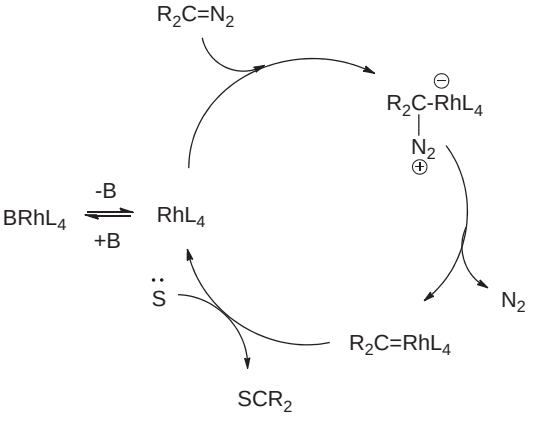
through alumina in those cases where epimerization was required.

In case of the recycling experiment, a 3.5-mL high-pressure cell was charged with diazoacetamide (0.173 mmol) and dirhodium (II) complex (1 mol%) and placed inside a constant temperature water bath. $CO_2$ was introduced into the cell by a screw injector pump, at a constant temperature of 30°C. The mixture was stirred with a magnetic stirrer for 24 hours under 30°C and 70 bar. Subsequently, supercritical extraction was performed at a constant pressure of 170 bar and 40°C. The extraction was considered finished when 0.35 mol of $CO_2$, corresponding to displacing 19 $cm^3$ of the volume of the screw injector pump, had passed through the system. The product was collected in cold traps filled with dichloromethane and cooled by a (ice + sodium chloride) mixture. After this, the system was depressurized, and a fresh quantity of diazoacetamide (0.173 mmol) was added to the dirhodium(II) complex that remained in the cell after the extraction.

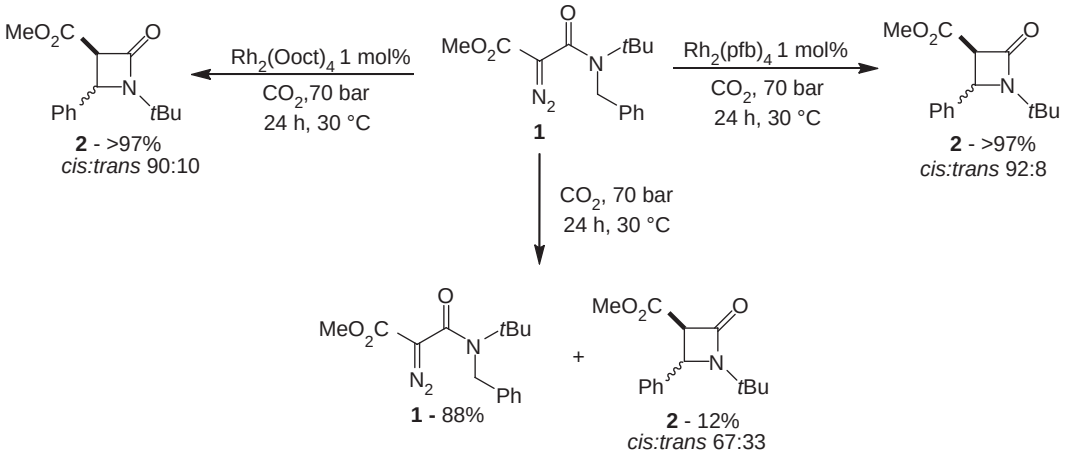
High-performance liquid chromatography data: The enantiomeric excess of **14** was determined using a Chiralcel column in the following conditions: Chiralpak AD column, Hexane/iso-Propanol 97:3, 0.7 mL/min, 225 nm, Rt = 11.3 min (major), and Rt = 13.1 min (minor).

## Results and discussion

*sc*$CO_2$ has many advantages as a solvent for homogeneous catalysis, namely it permits a very rapid mass transfer, it is completely miscible with gaseous reactants, and is easy to remove from the product and at the same timeallows the catalyst/product separation(*26–28*). Apart from this, it is nontoxic, nonflammable, and nonpolluting(*29,30*). The low solubilizing ability of *sc*$CO_2$ and its reactivity in some conditions have been frequently pointed as disadvantages associated with the use of this supercritical fluid(*31*). Nevertheless, over the years *sc*$CO_2$ has been successfully used as solvent in many homogeneously metal-catalyzed reactions (*26–31*). Despite this, and as far as our knowledge goes, the intramolecular or intermolecular C–H insertion with diazo compounds catalyzed by dirhodium(II) complexes has never been reported in this media, differently the asymmetric cyclopropanation with a chiral

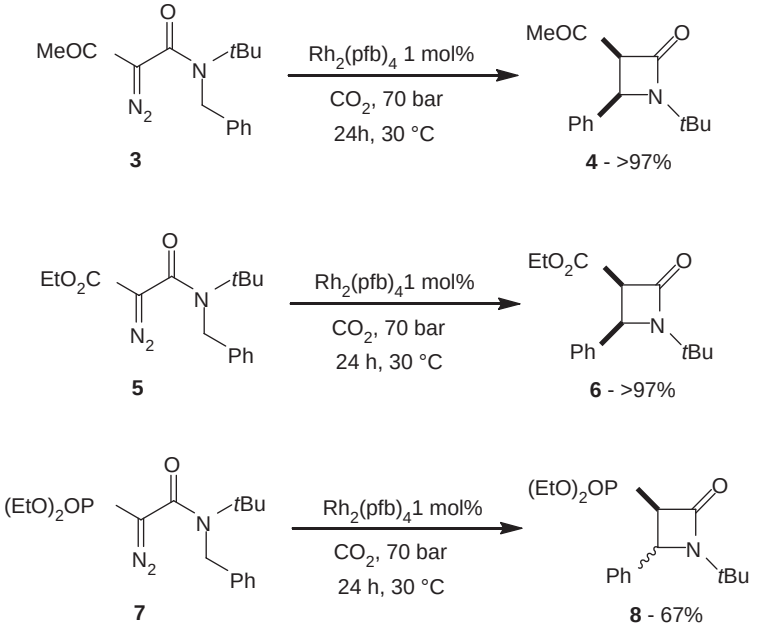



Scheme 1. General mechanism for the generation of metallocarbenes from diazo compounds and dirhodium(II) complexes.



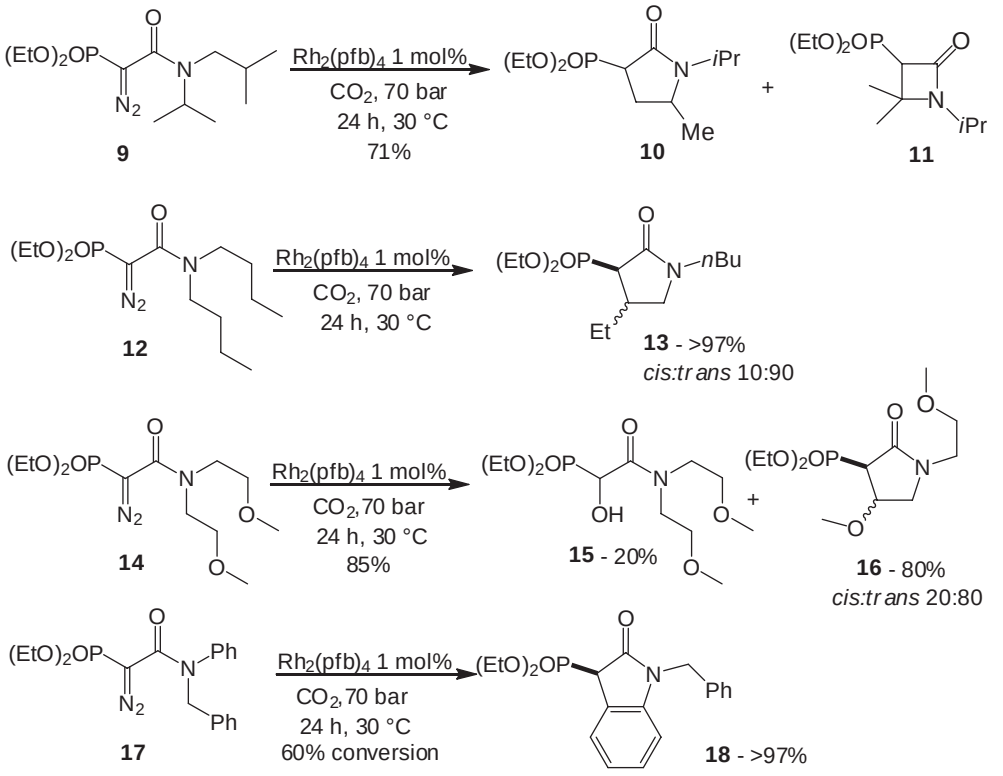

Scheme 2. Intramolecular C–H insertion of diazoacetamide 1 using dirhodium(II) complexes in $CO_2$ (70 bar). Conversions and *cis:trans* stereoselectivities determined based on $^1$H-NMR.

dirhodium(II) complexes in *sc*$CO_2$ was described by Jessop and colleagues (*32*). Encouraged by this precedent, we initiated our study by evaluating the cyclization of diazoacetamide **1**. Very gratifyingly, when performing the reaction between diazoacetamide **1** with $Rh_2(pfb)_4$ (tetratkis perfluorobutanoate di-rhodium(II)) at 30°C and 70 bar of $CO_2$ for 24 hours, *cis*-β-lactam **2** was obtained quantitatively either using the perfluorinated dirhodium(II) complex ($Rh_2(pfb)_4$) or a complex featuring octanoate as the




| Solvent | Temp. | Time | Catalyst | *cis:trans* |
|---|---|---|---|---|
| $CO_2$ | 30 °C | 24 h | $Rh_2(pfb)_4$ | *cis:trans* 93:7 |
| $H_2O$ | 80 °C | 24 h | $Rh_2(pfb)_4$ | *cis:trans* 62:38 |
| $CH_2Cl_2$ | reflux | 7 h | $Rh_2OAc)_4$ | *cis:trans* 88:12 |
| Hexane | r.t. | 24 h | h | *cis:trans* 33:67 |

Scheme 3. Intramolecular C–H insertion of diazoacetamides 3, 5, and 7 using $Rh_2(pfb)_4$ in $CO_2$ (70 bar). Conversions and *cis:trans* stereoselectivities were determined based on $^1$H- and $^{31}$P-NMR.



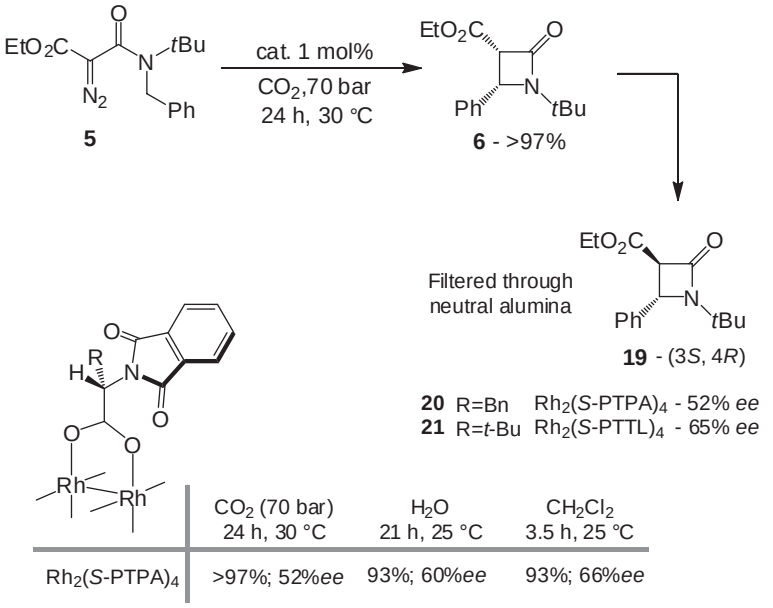

Scheme 4. Intramolecular C–H insertion of phosphoryl diazoacetamides 9, 12, 14, and 17 using $Rh_2(pfb)_4$ in $CO_2$ (70 bar). Conversions and *cis:trans* stereoselectivities were determined based on $^{31}$P-NMR.

dirhodium(II) bridging ligands ($Rh_2(Ooct)_4$ – (tetratkis octanoate di-rhodium(II)). As expected, in the presence of $CO_2$ but without catalyst, only 12% of the lactam was formed. This is probably due to the presence of trace amounts of catalyst absorbed onto the container walls (Scheme 2).

Taking into consideration the results obtained in the cyclization of substrate **1**, we evaluated the C–H insertion catalyzed by $Rh_2(pfb)_4$ of diazoacetamides **3**, **5**, and **7** bearing different α-substituents (Scheme 3). The cyclization of diazoacetamides **3** and **5** afforded exclusively the *cis*-β-lactam, although the presence of a bulkier and more hydrophilic phosphoryl group resulted in a less selective transformation of **7** and the lactam **8** was obtained in 67%. Despite this, the diastereoselectivity obtained in the cyclization of **7** in $CO_2$ compares favorably with the results obtained in $CH_2Cl_2$, water, or under photochemical conditions (*23–25*)(*34–38*).

Once we confirmed the possibility of preparing β-lactams from diazoacetamides in $CO_2$, we next studied the synthesis of five-membered rings in this media. As shown in Scheme 4, different phosphoryl diazoacetamides successfully underwent the C–H insertion in the presence of $Rh_2(pfb)_4$ to form the expected lactams in good yields. Diazoacetamide **9** afforded the β-lactam in 71% and traces of lactam 10. Substrate **12** reacted to form lactam **13** in over 97% yield, while the cyclization of substrate **14** afforded lactam **16** in 80% and 20% of alcohol **15**. The formation of the alcohol is probably due to the hygroscopic nature of this compound and the presence of water molecules nearby the metallocarbenoid center. The alcohol is formed exclusively when performing the cyclization of this compound in water as we observed in our previous studies on the use of water, as solvent for this reaction (*23–25*). In the case of substrate 17, the cyclization afforded only lactam 18, although 40% of the starting diazo compound remained unreacted. This may be due to the fact that oxindole **18** is probably obtained *via* the aromatic substitution pathway which is thought to proceed through an electrophilic attack of the metallocarbenoid carbon atom on the aromatic ring followed by a 1,2-hydride shift with a concomitant dissociation of the catalyst and subsequent aromatization, rather than *via* a direct C–H insertion (*11*). Therefore, the lower yield obtained in $CO_2$ may result from a lower solvent stabilization of the zwitterionic intermediate on the aromatic substitution.

Once we confirmed the possibility of performing the C–H insertion of diazoacetamides in $CO_2$, we tested the asymmetric version of this process using chiral dirhodium(II) complexes (Scheme 5). We were



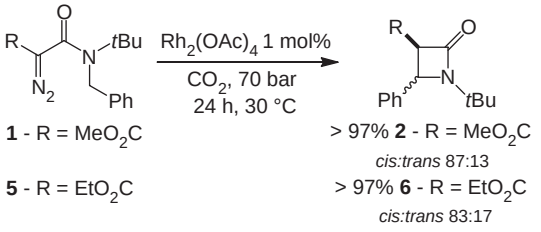

Scheme 5. Asymmetric intramolecular C–H insertion of diazoacetamide 5 in $CO_2$ (70 bar). The conversion and diastereoselectivity were determined by $^1$H-NMR, and the enantioselectivity was determined by chiral HPLC (Chiralpak AD column, Hexane/iso-Propanol 97:3, 0.7 mL/min, 225 nm, Rt = 11.3 min (major), Rt = 13.1 min (minor)).

delighted to observe that β-lactam **6** was formed quantitatively with 52% and 65% *ee* after epimerization in basic alumina using 20 and 21, respectively. Comparing with the results obtained in chlorinated solvents and in water, the observed enantiomeric excesses are only slightly lower in $CO_2$ (Scheme 5).

Finally, we tested the possibility of performing the catalyst/product separation based on the extraction using $CO_2$. In order to improve the putative separation, we envisioned that a dirhodium(II) complex with a lower fluorine content would be less soluble in the $CO_2$ phase and consequently would be less extracted. Therefore, we performed the cyclization of **1** and **5** catalyzed by $Rh_2(OAc)_4$. Very gratifyingly, both cyclizations afforded the expected β-lactams exclusively as shown in Scheme 6. Taking this result into consideration, we conceived a recycling experiment in which the substrate was submitted to a C–H insertion catalyzed by $Rh_2(OAc)_4$ in $CO_2$, followed by extraction and new addition of substrate as shown in Figure 1. As expected, using diazoacetamide **5** the first cyclization took place in high yield and lactam **6** was recovered in 75% yield, after extraction with $CO_2$ at 170 bar and 40°C. In order to understand if the catalyst remaining in the cell could still catalyze the reaction, a new substrate was added. Very gratifyingly, this second reaction afforded lactam **6** quantitatively and confirmed that the $Rh_2(OAc)_4$ complex endured the extraction protocol retaining its catalytic activity. This final reaction highlighted that the C–H insertion of diazoacetamides proceeds very successfully using $CO_2$ as solvent and that the extraction with *sc*$CO_2$ may indeed allow the catalyst reutilization and at the same time reduces the use of organic solvents in the isolation process.

## Conclusion

We have established the intramolecular C–H insertion of diazoacetamide using $CO_2$ as a solvent. This




Scheme 6. Intramolecular C–H insertion of diazoacetamides 1 and 5 in $CO_2$ (70 bar) using $Rh_2(OAc)_4$. Conversions and stereoselectivities were determined based on $^1$H-NMR.

process afforded the expected lactams in yields over 97%. The asymmetric intramolecular C–H insertion was also achieved, and β-lactam **19** was obtained in >97% yield and 65% *ee* using the chiral dirhodium(II) catalyst $Rh_2$(*S*-PTTL)$_4$. Finally, the dirhodium(II) complex $Rh_2(OAc)_4$ was used in two consecutive cycles in which complete conversion to the lactam was obtained. This recycling experiment demonstrated that $CO_2$ can be used as an efficient solvent for C–H insertions based on diazo compounds/dirhodium(II) complexes and that the extraction with *sc*$CO_2$ may indeed allow the catalyst reutilization and at the same time reduces the use of organic solvents in the isolation process.

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## SUPPORTING INFORMATION

### *General Remarks*

Preparative thin layer chromatography plates were prepared with silica gel 60 GF254 MercK (Ref. 1.07730.1000). Reaction mixtures were analysed by TLC using ALUGRAM® SIL G/UV254 from MN (Ref. 818133, silica gel 60), and visualisation of TLC spots was effected using UV and $KMnO_4$ solution. NMR spectra were recorded in a Bruker AMX 400 using $CDCl_3$ as solvent and $(CH_3)_4Si$ (1H) as internal standard. All coupling constants are expressed in Hz. Dirhodium(II) complexes: tetracetate, perfluorobutyrate and octanoate complexes were purchased from Aldrich and $Rh_2$(*S*-PTPA)$_4$ and $Rh_2$(*S*-PTTL)$_4$ were prepared accordingly with reported procedures [1,2]. The diazoacetamides: 1, 3, 5, 7, 9, 12, 14 and 17 were prepared according with reported procedures [3–5]. Lactam 2 was obtained as characterized in reference [3], lactams 8, 11, 13 and 16 in reference [4], lactams 6 and 18 and hydroxy acetamide 15 in reference [5].

### *General procedure for the cyclisation of diazoacetamide with dirhodium(II) complexes in $CO_2$*

A 3.5 mL high-pressure cell was charged with diazoacetamide (0.173 mmol) and dirhodium (II) complex (1 mol%) and placed inside a constant temperature water bath. $CO_2$ was introduced into the cell by a screw injector pump, at a constant temperature of 30°C. The mixture was stirred with a magnetic stirrer for 24 hours under 30°C and 70 bar. After which the system was depressurised and the conversions and *cis:trans* stereoselectivities determined based on $^1$H or $^{31}$P NMR. In specific cases, the product was filtered through basic alumina in order to epimerize the product form from cis to trans.

In the case of the recycling experiment: a 3.5-mL high-pressure cell was charged with diazoacetamide (0.173 mmol) and dirhodium (II) complex (1 mol%) and placed inside a constant temperature water bath. $CO_2$ was introduced to the cell by a screw injector pump, at a constant temperature of 30°C. The mixture was stirred with a magnetic stirrer for 24 hours under 30°C and 70 bar. Subsequently, supercritical extraction was performed at a constant pressure of 170 bar and 40°C. The extraction was considered finished when 0.35 mol of $CO_2$, corresponding to displacing 19 $cm^3$ of the volume of the screw injector pump, had passed through the system. The product was collected in cold traps filled with dichloromethane and cooled by a (ice + sodium chloride) mixture. After this, the system was depressurised and a fresh quantity of diazoacetamide (0.173 mmol) was added to the dirhodium(II) complex that remained in the cell after the extraction. The collected product purity was determined based on $^1$H NMR.

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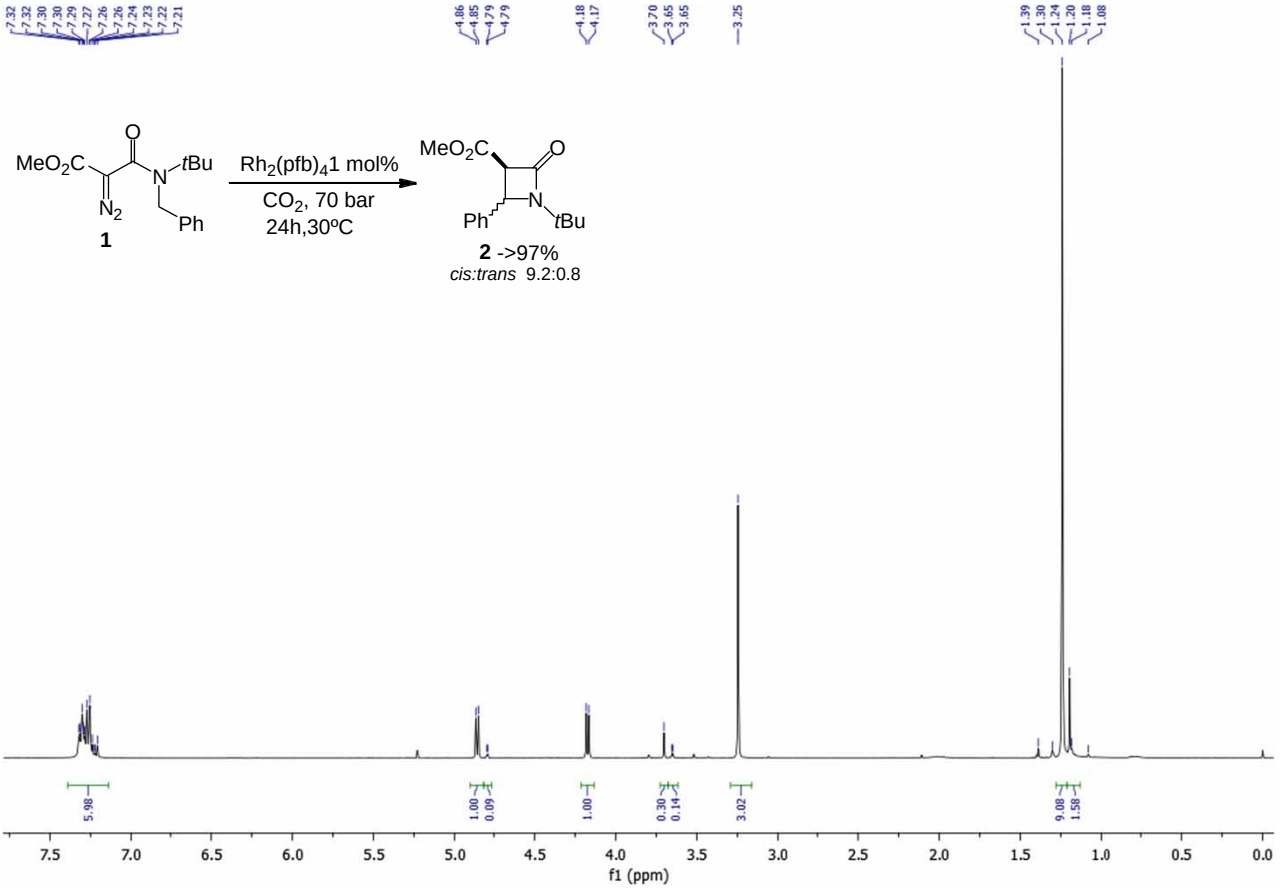
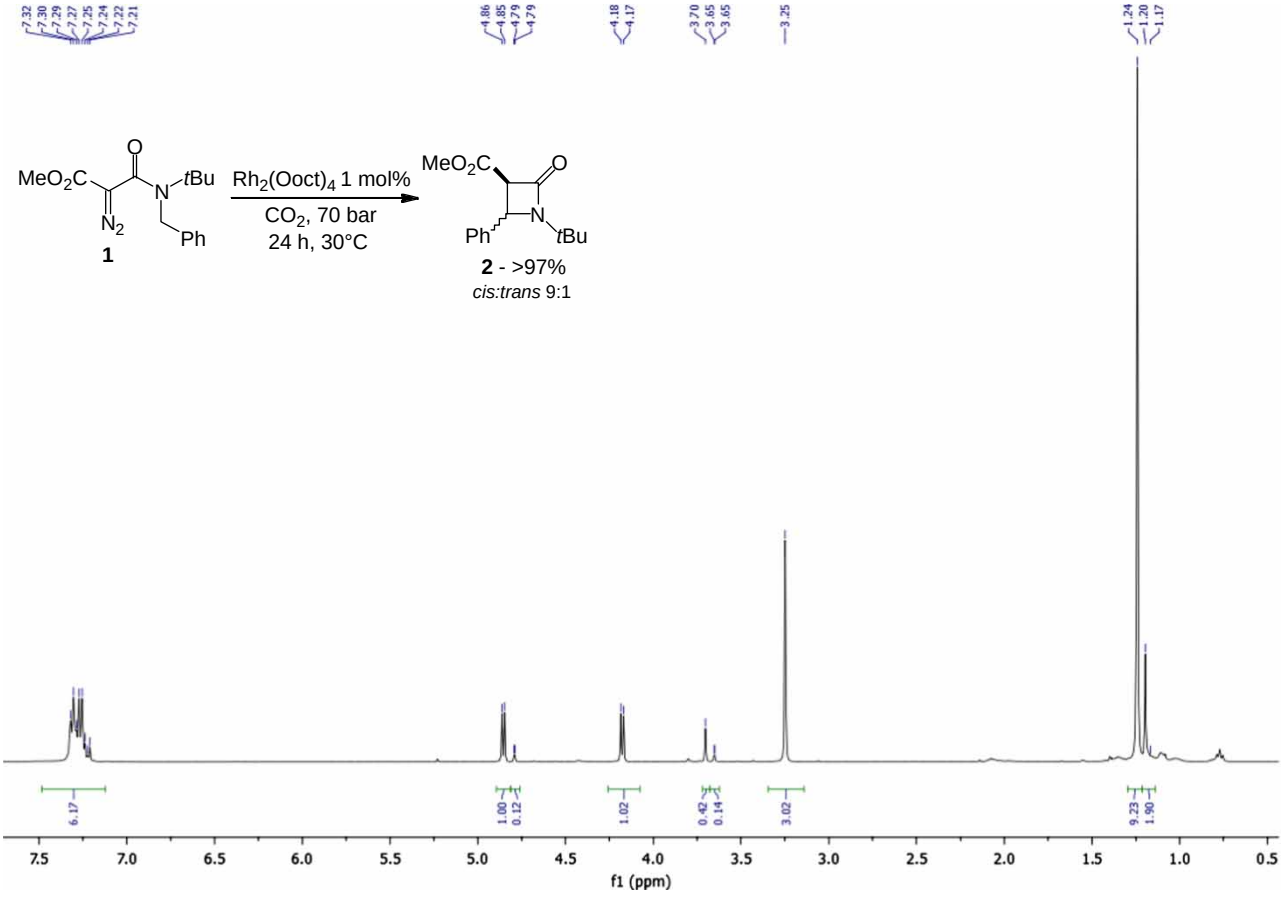
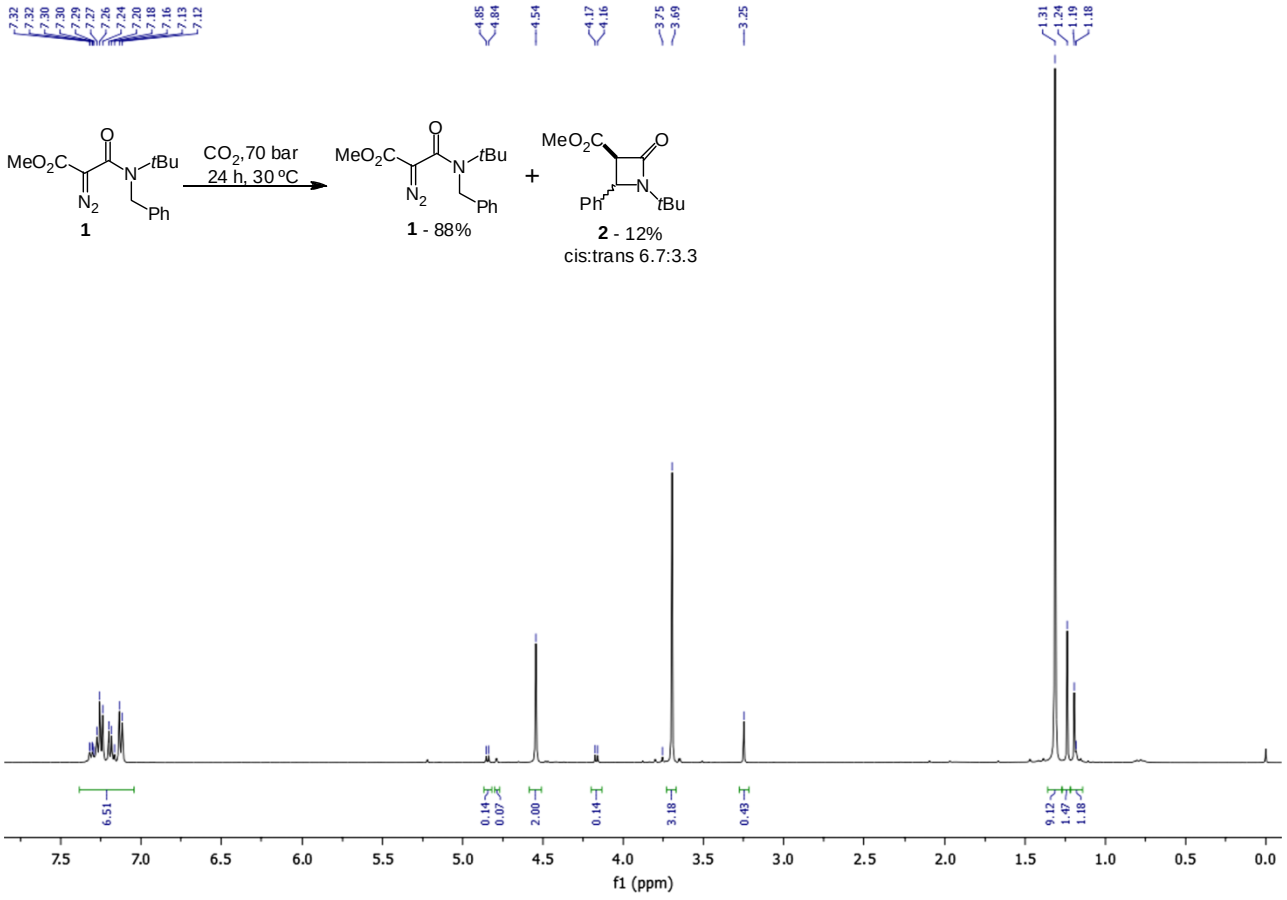


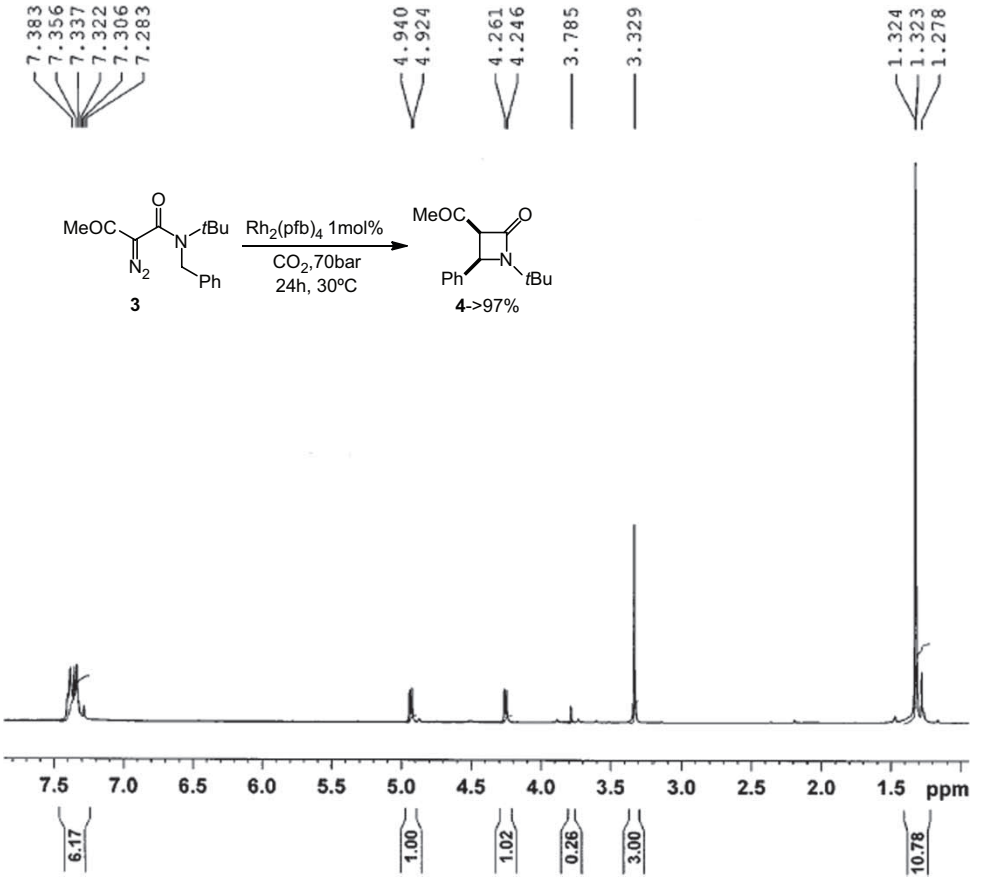

**Scheme S1**. – $^{1}$H NMR spectrum of crude cyclization reaction of 1 with $Rh_2(pfb)_4$.



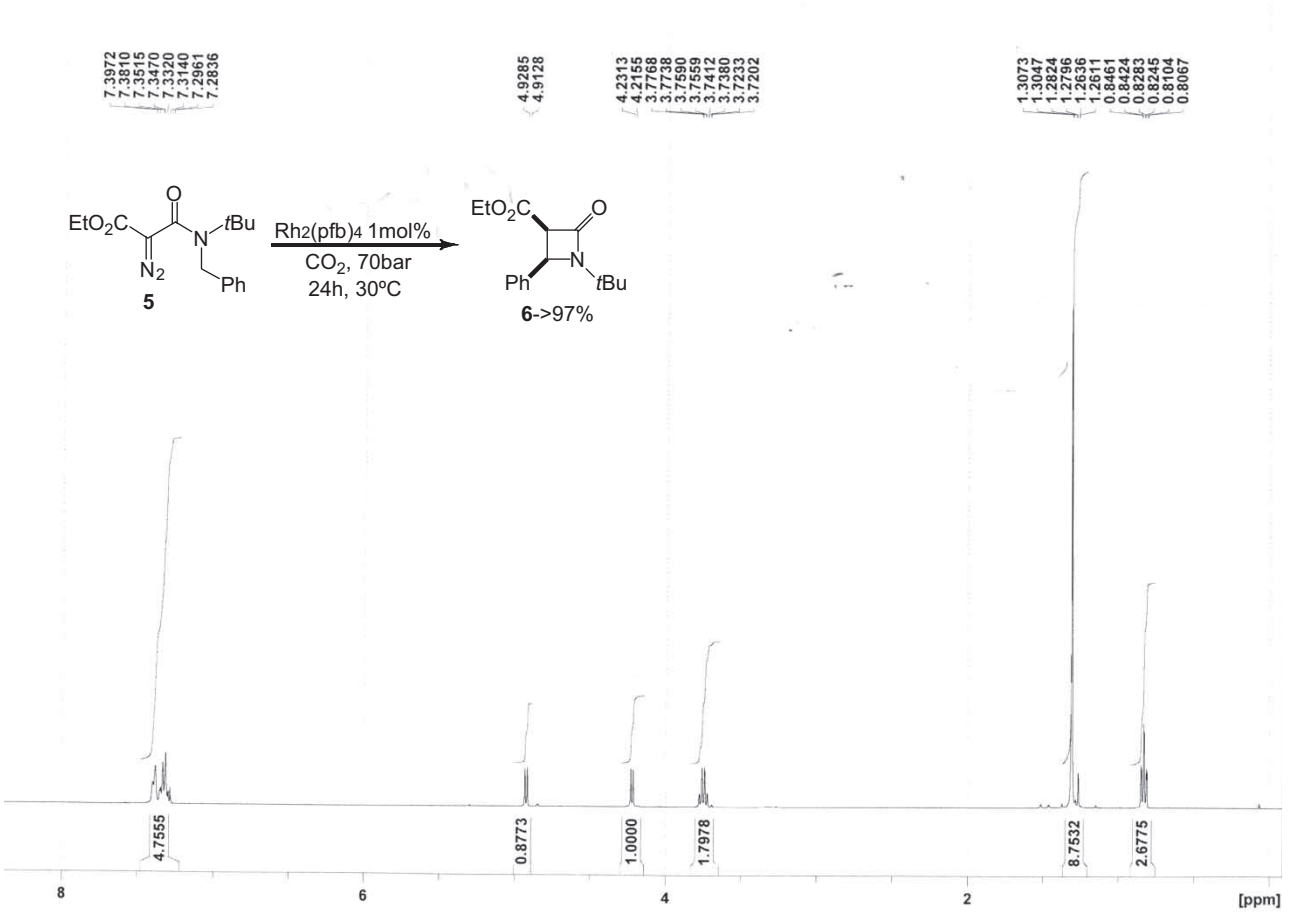

**Scheme S2**. – $^{1}$H NMR spectrum of crude cyclization reaction of 1 with $Rh_2(Oct)_4$.



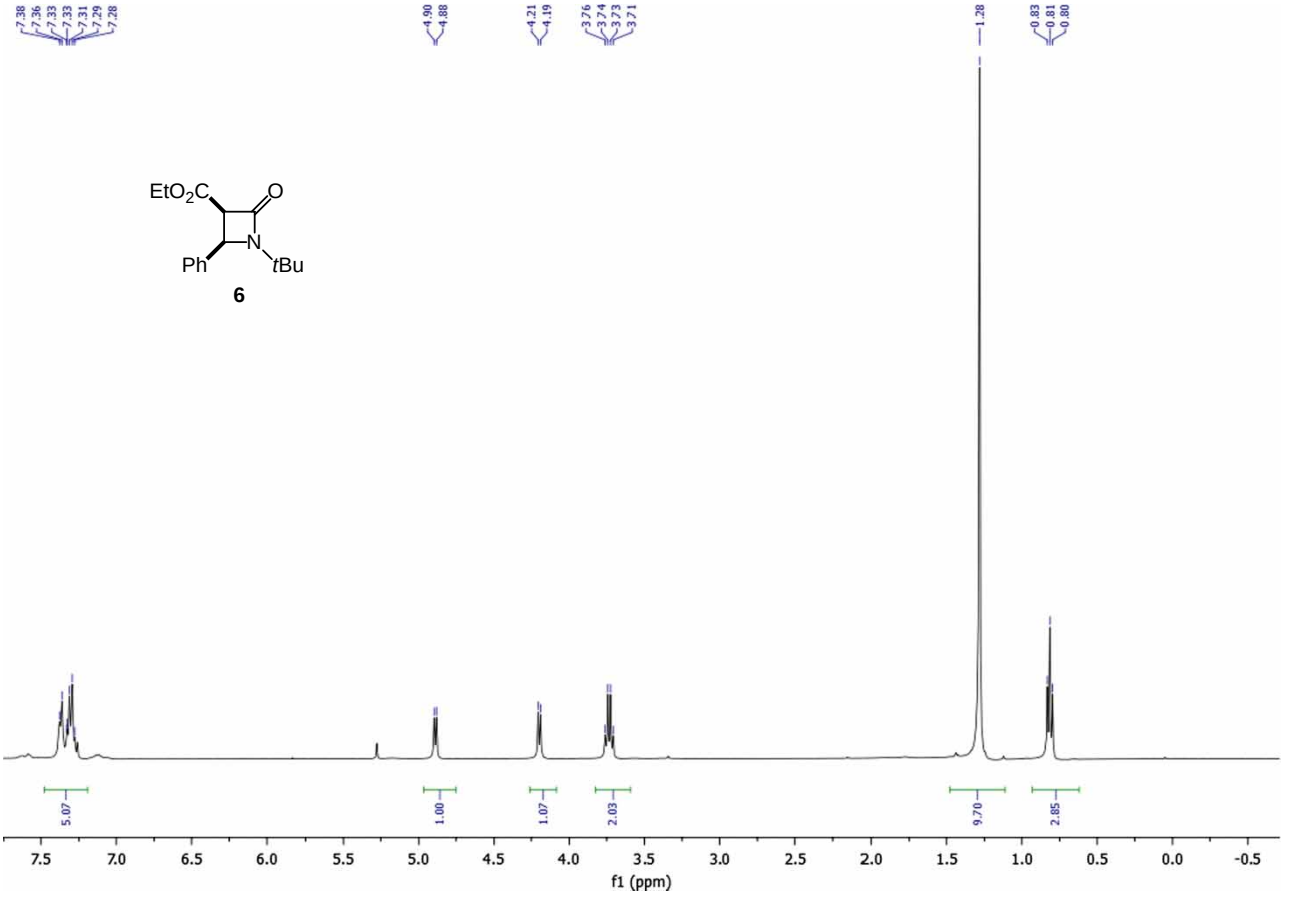

**Scheme S3**. – $^{1}$H NMR spectrum of control experiment of 1 without dirhodium catalyst.



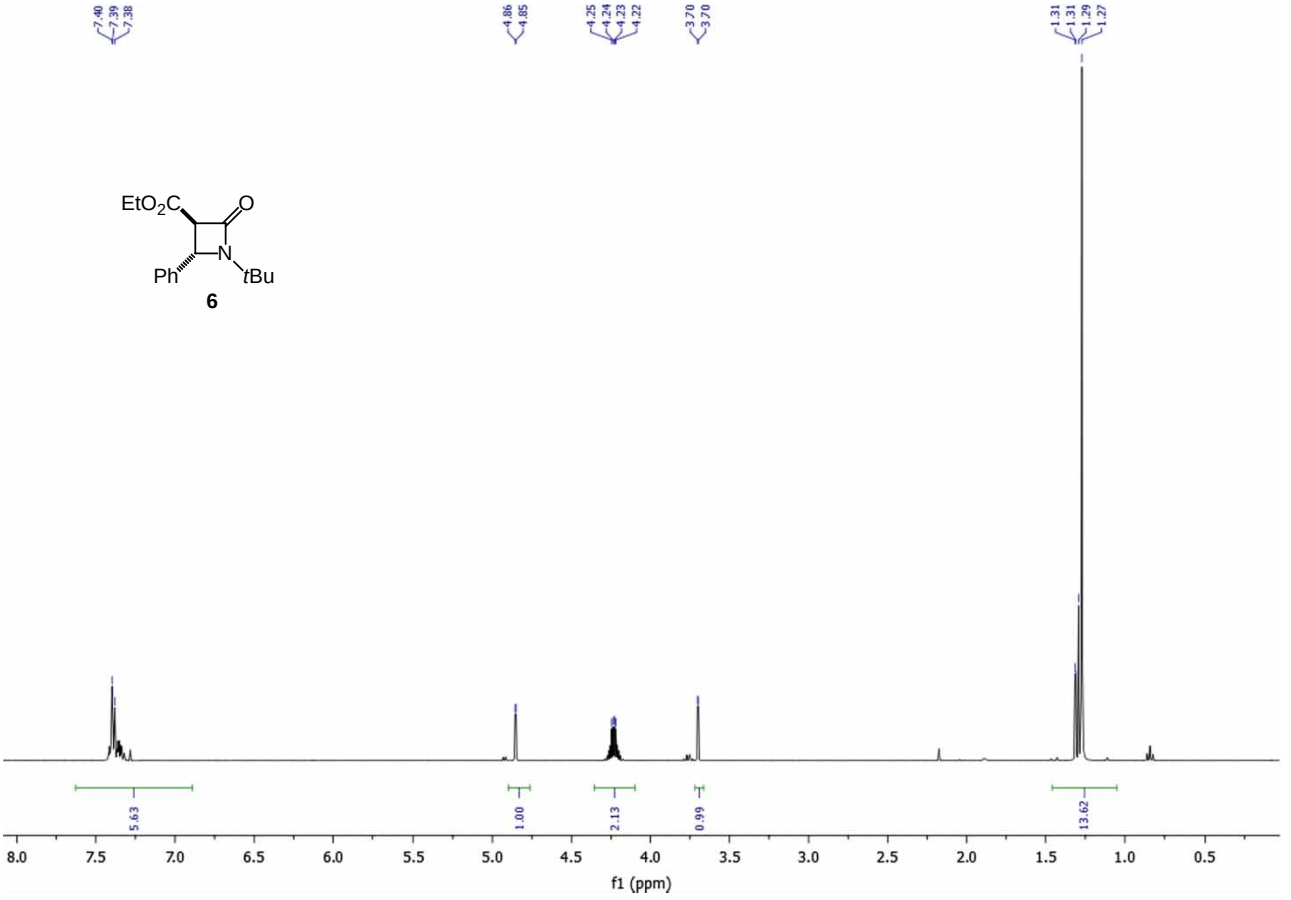

**Scheme S4**. – $^{1}$H NMR spectrum of crude cyclization reaction of 3 with $Rh_2(pfb)_4$.



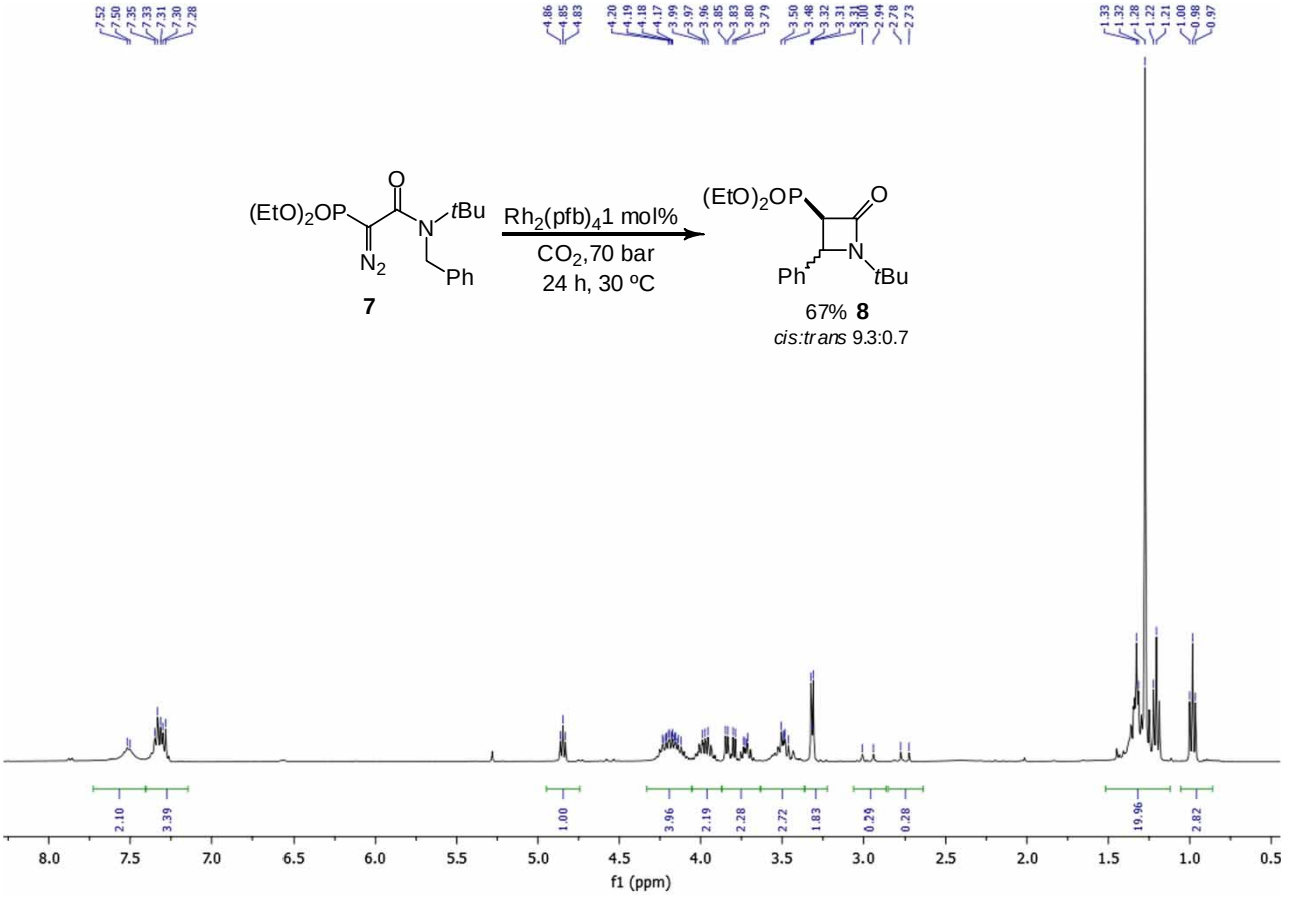

**Scheme S5**. – $^1$H NMR spectrum of crude cyclization reaction of 5 with $Rh_2(pfb)_4$.



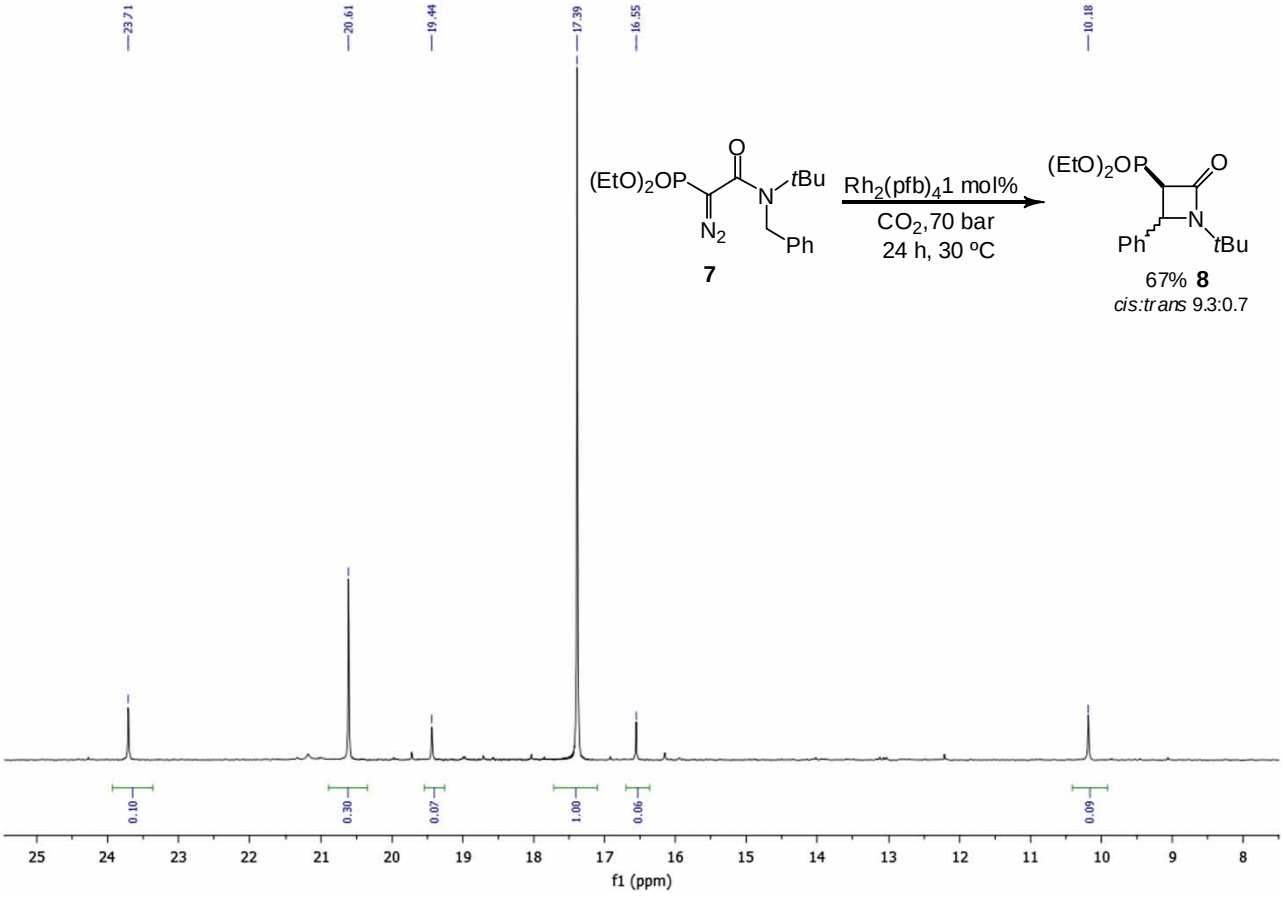

**Scheme S6**. – $^{1}$H NMR spectrum of isolated *cis*-lactam 6.



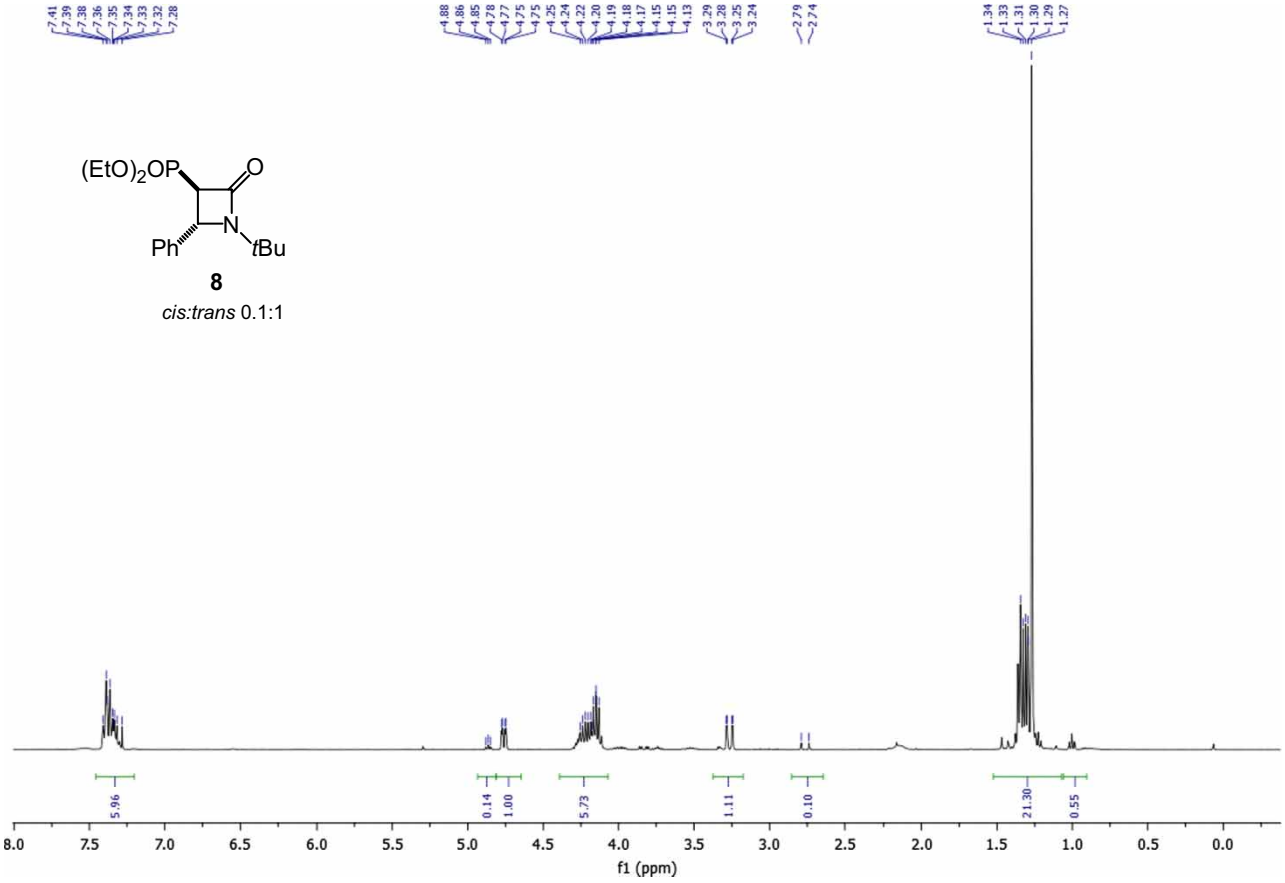

**Scheme S7**. – $^{1}$H NMR spectrum of isolated *trans*-lactam 6, epimerized by filtration of *cis*-lactam through neutral alumina.



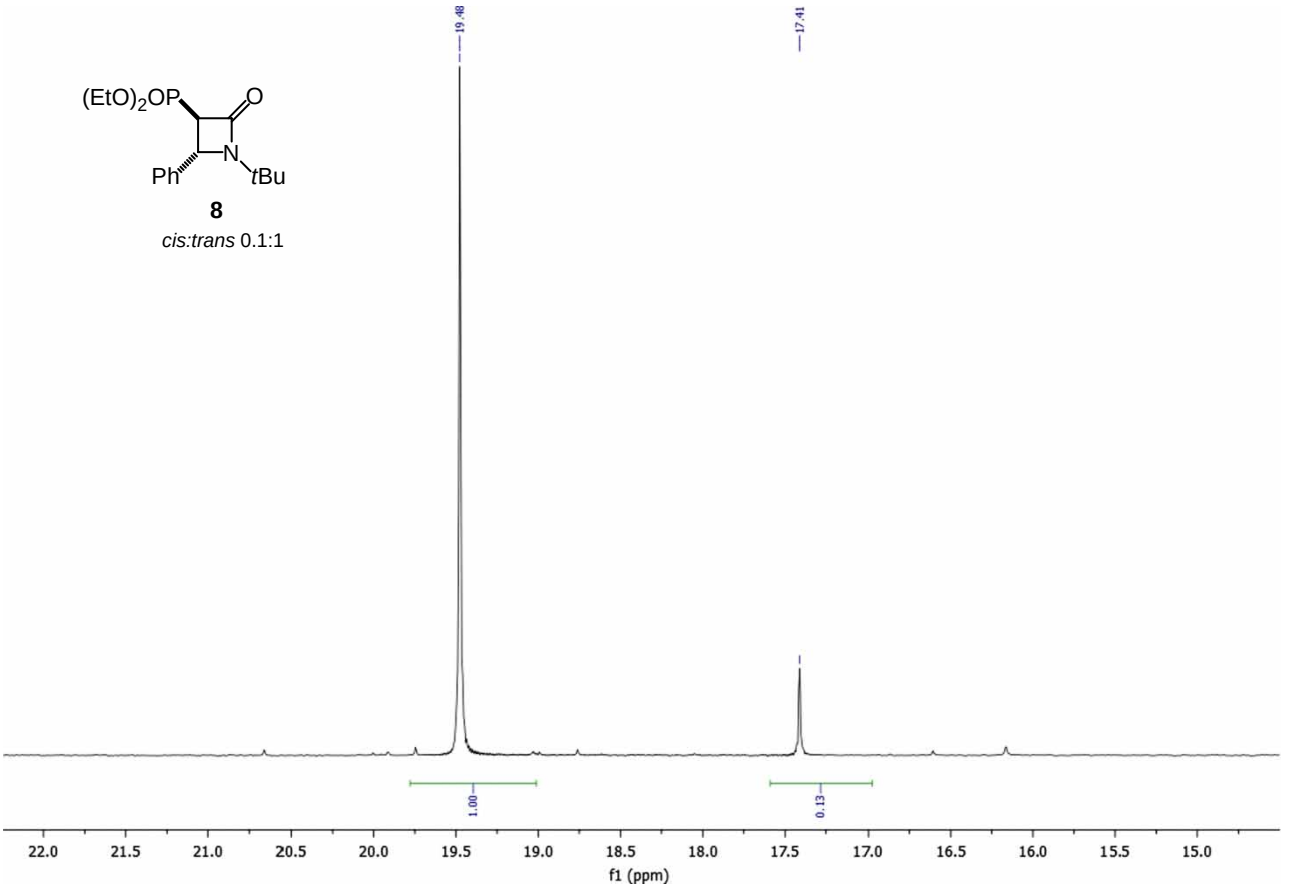

**Scheme S8**. – $^{1}$H NMR spectrum of crude cyclization reaction of 7.



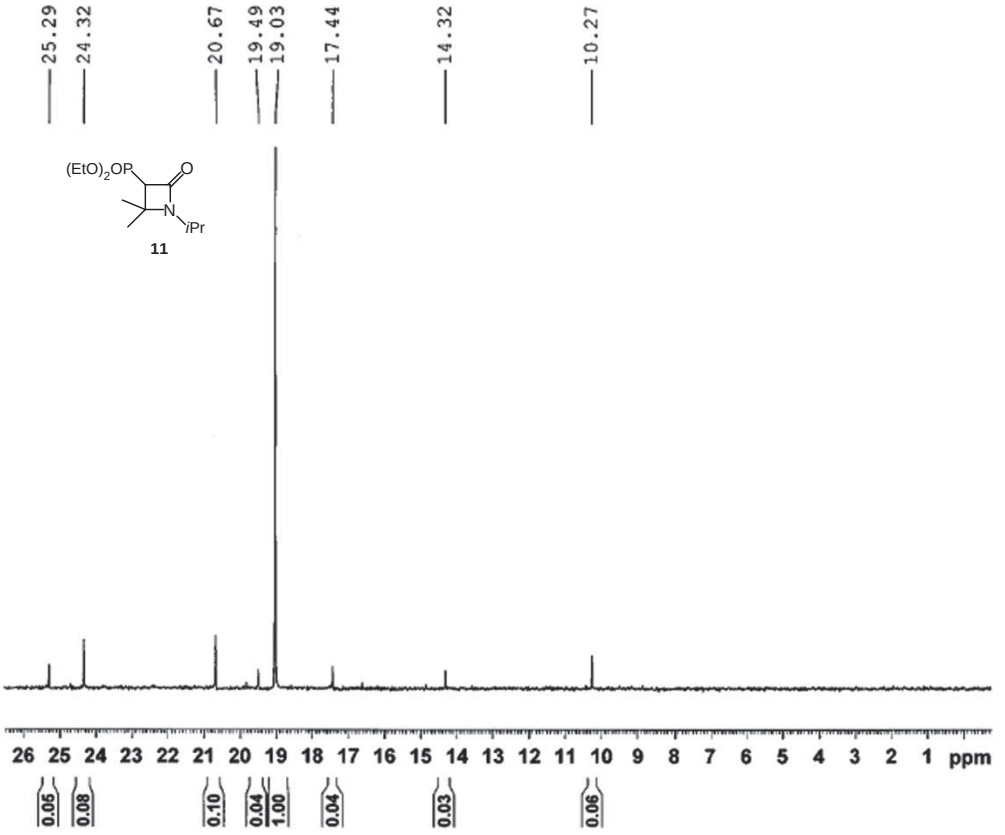

**Scheme S9**. – $^{31}$P NMR spectrum of crude cyclization reaction of 7.



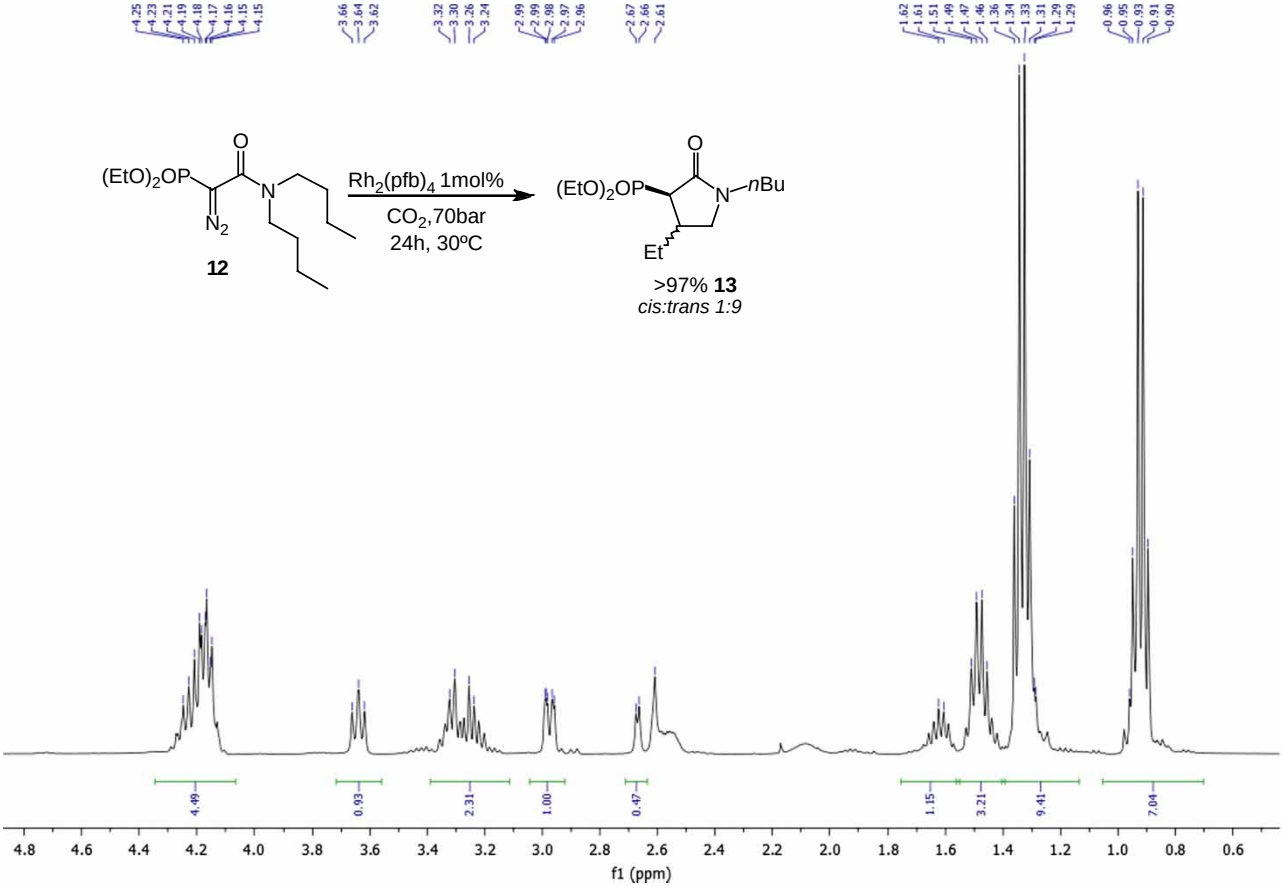

**Scheme S10**. – $^{1}$H NMR spectrum of isolated lactam 8 (after filtration through basic alumina).



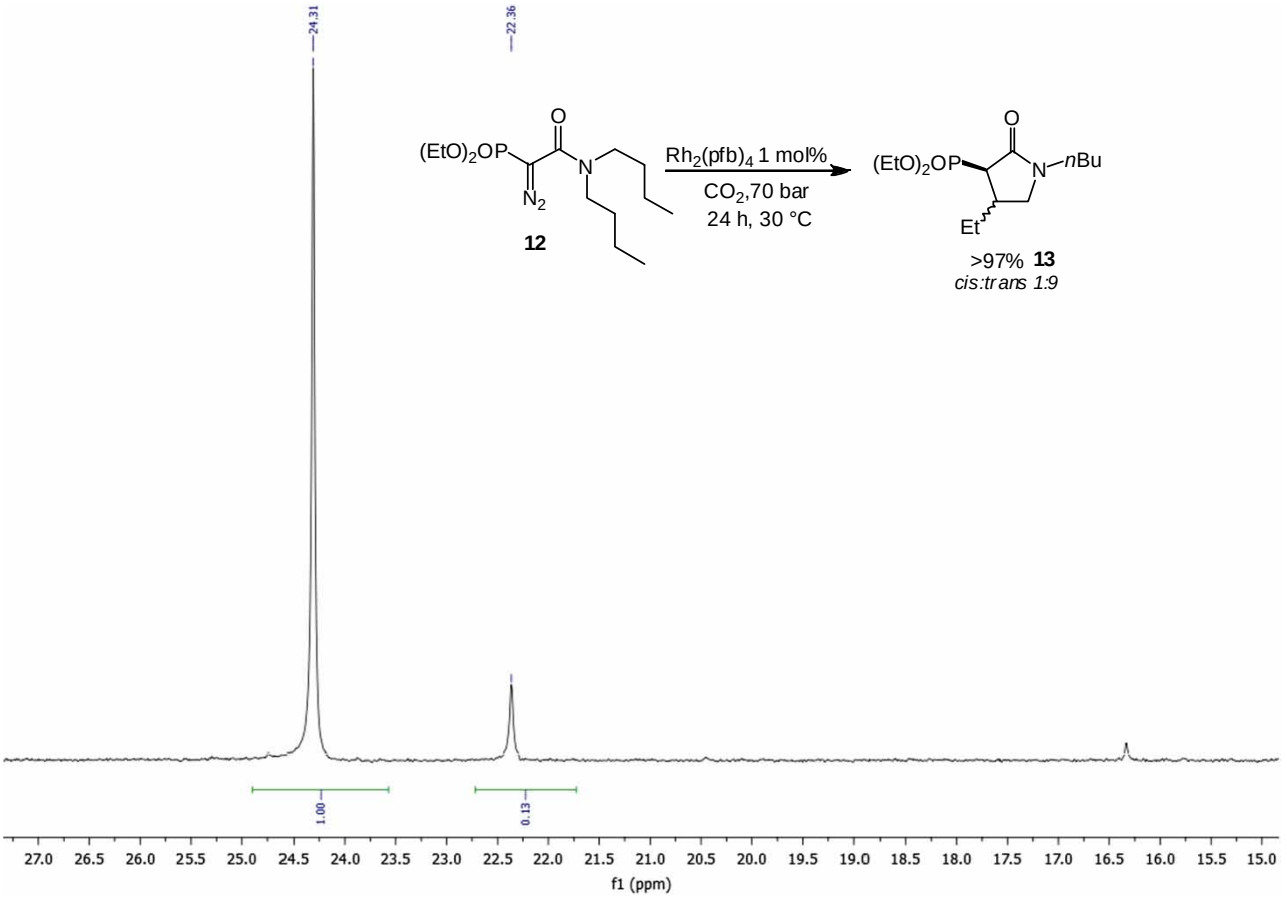

**Scheme S11**. – $^{31}$P NMR spectrum of isolated lactam 8 (after filtration through basic alumina).



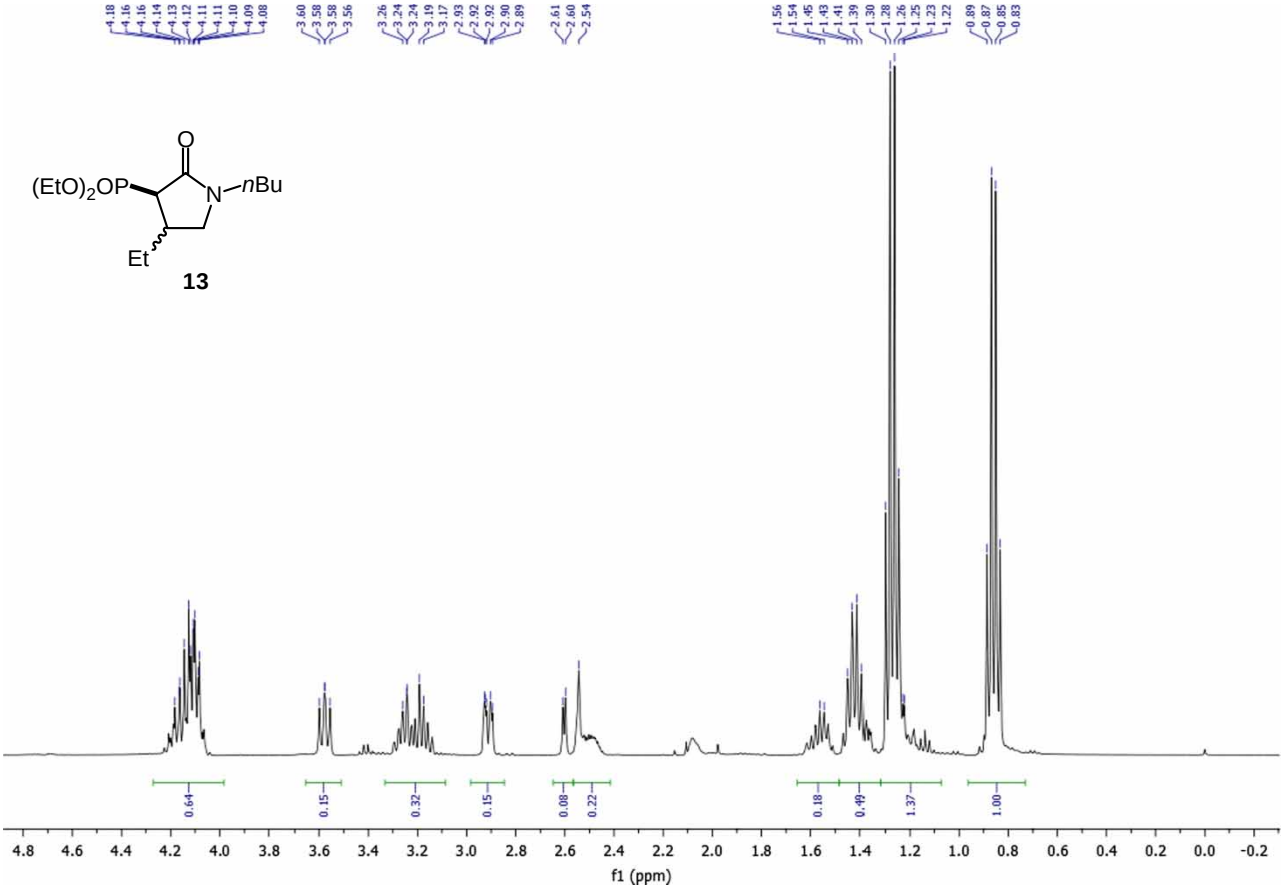

**Scheme S12**. – $^{31}$P NMR spectrum of isolated lactam 11 (after filtration through basic alumina).



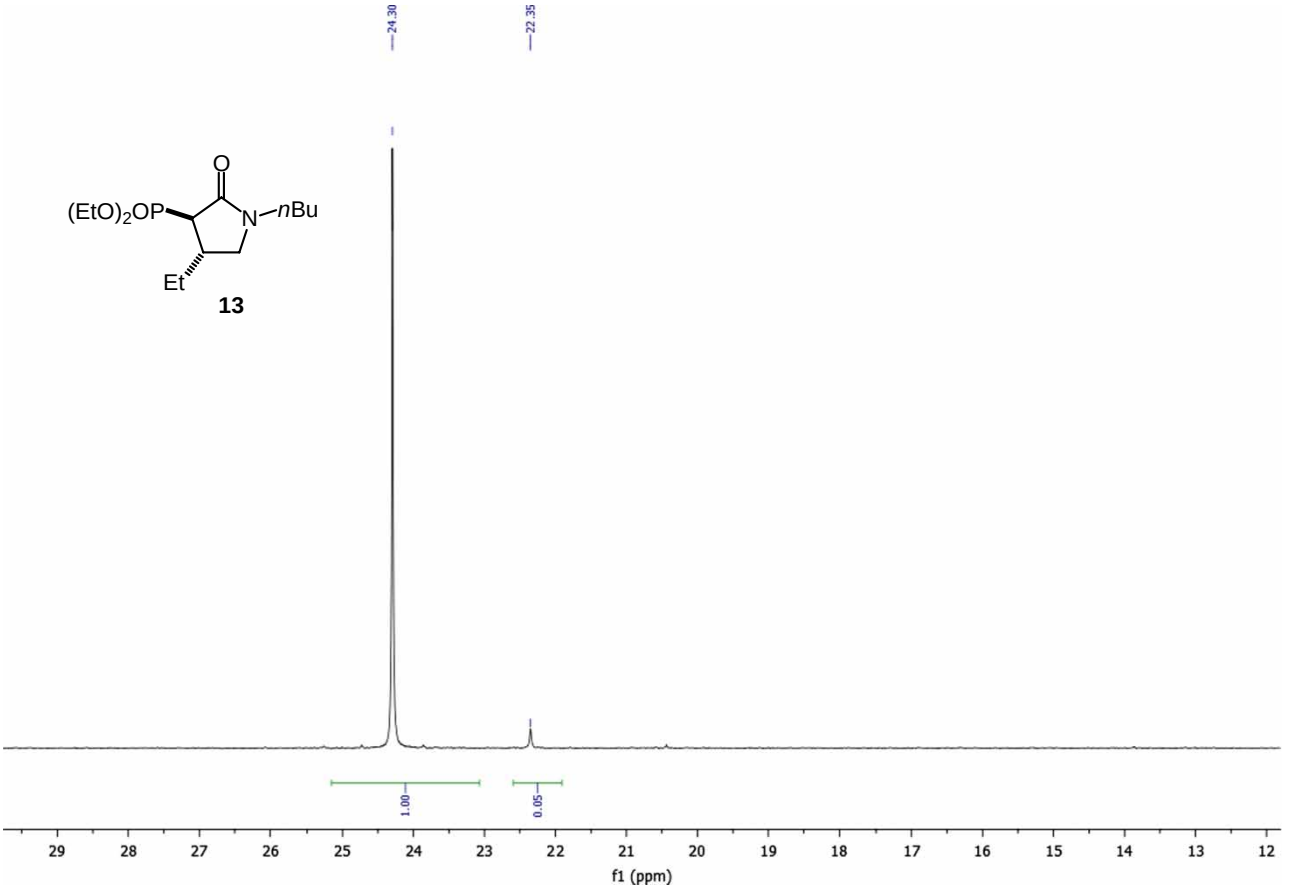

**Scheme S13**. – $^{1}$H NMR spectrum of crude cyclization reaction of 12.



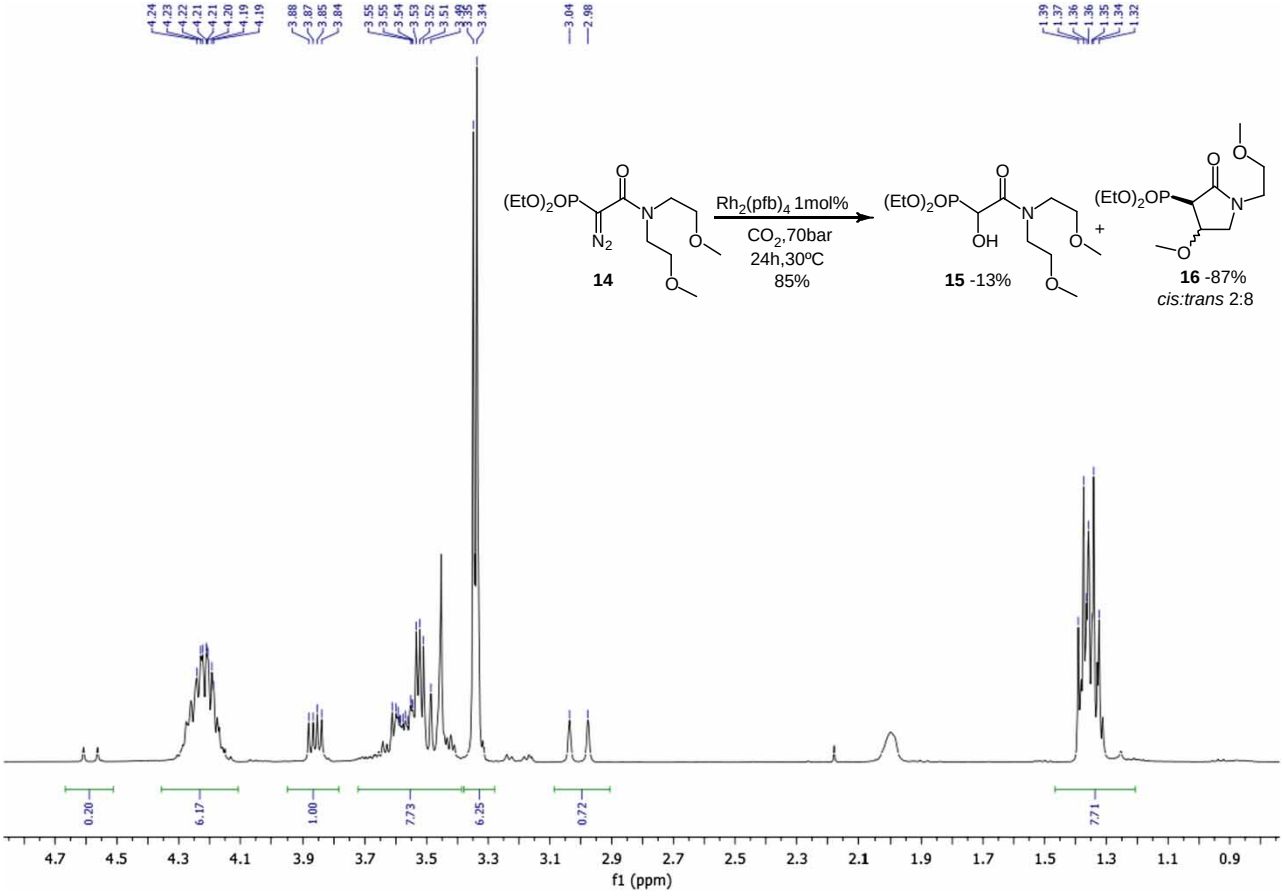

**Scheme S14**. – $^{31}$P NMR spectrum of crude cyclization reaction of 12.



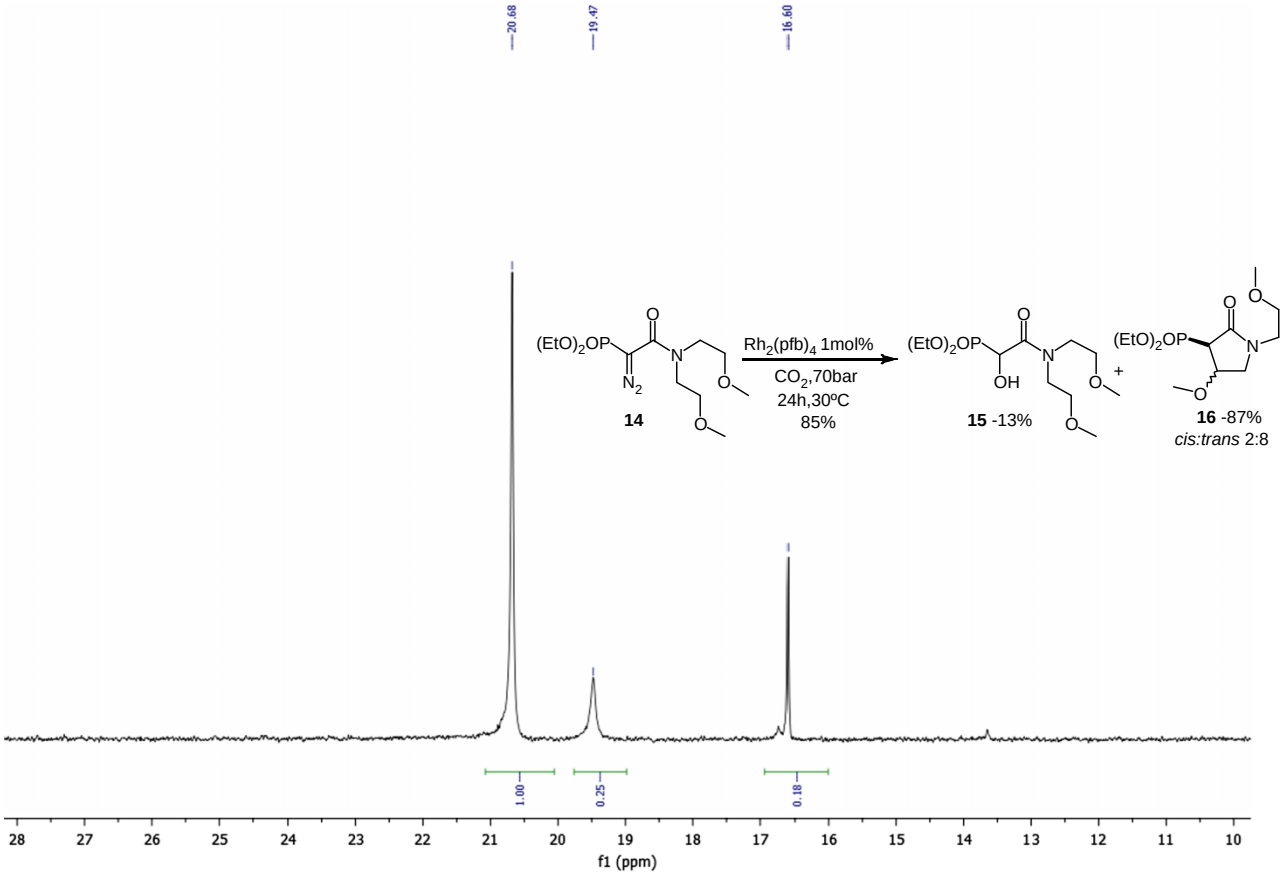

**Scheme S15**. – $^{1}$H NMR spectrum of isolated lactam 13 (after filtration through basic alumina).



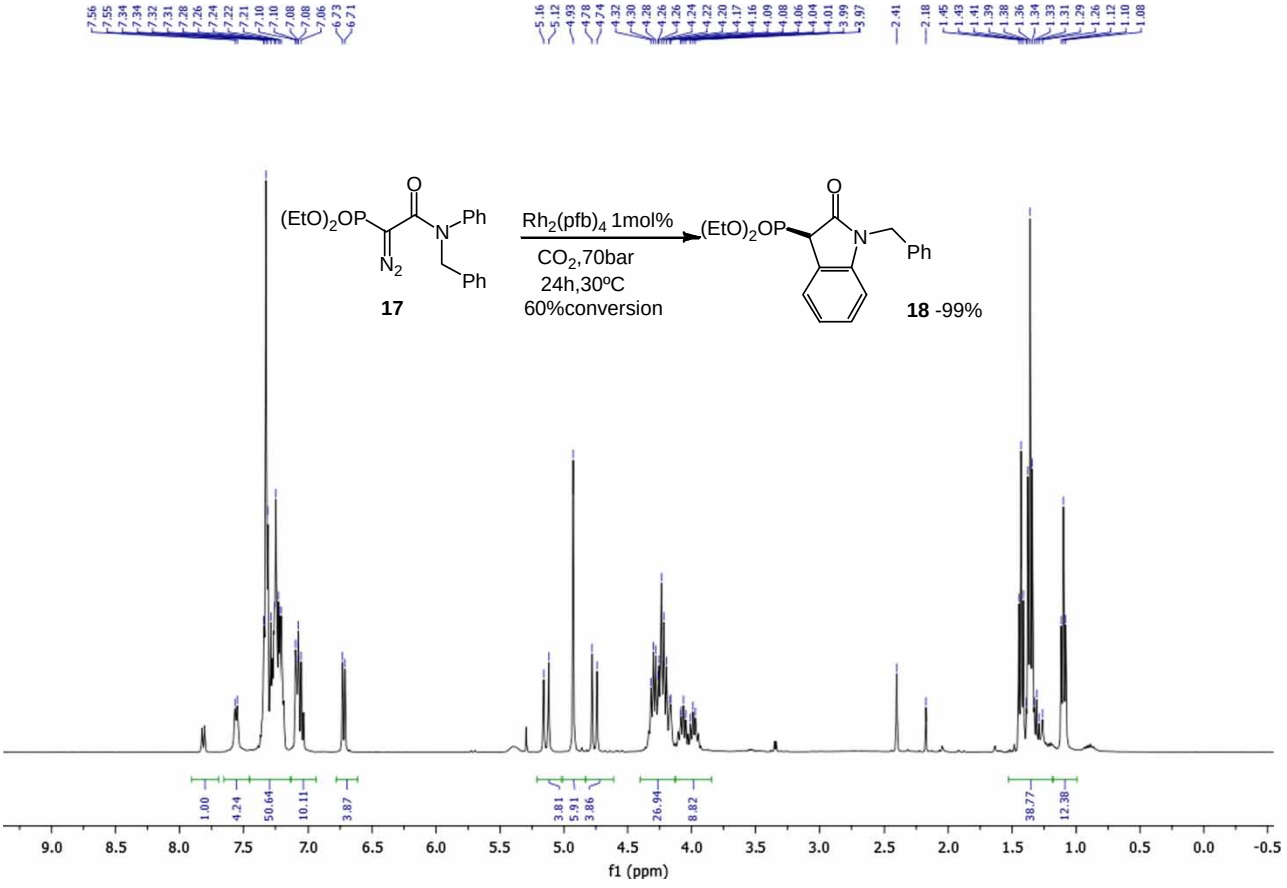

**Scheme S16**. $^{31}$P NMR spectrum of isolated lactam 13 (after filtration through basic alumina).



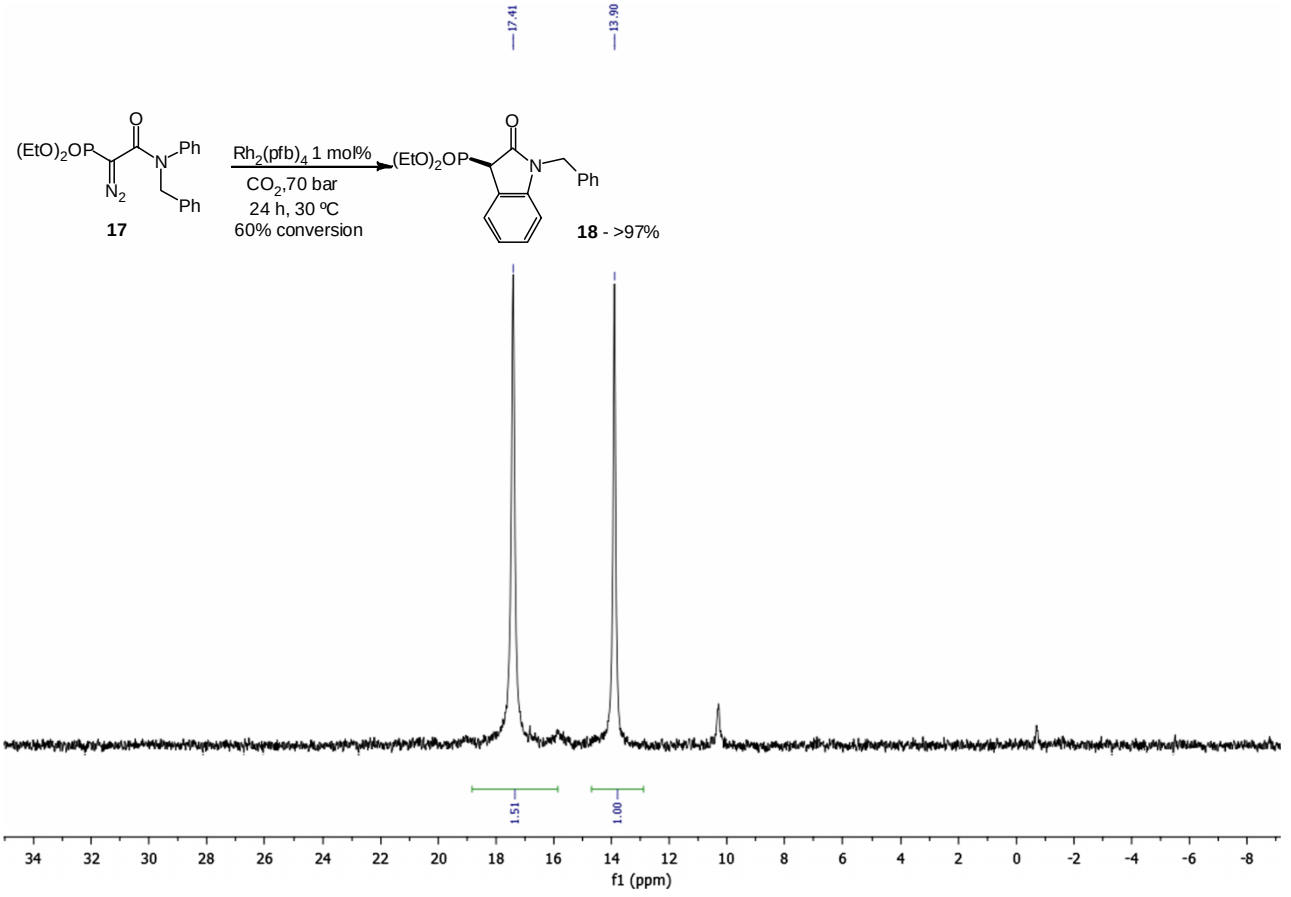

**Scheme S17**. – $^{1}$H NMR spectrum of crude cyclization reaction of 14.



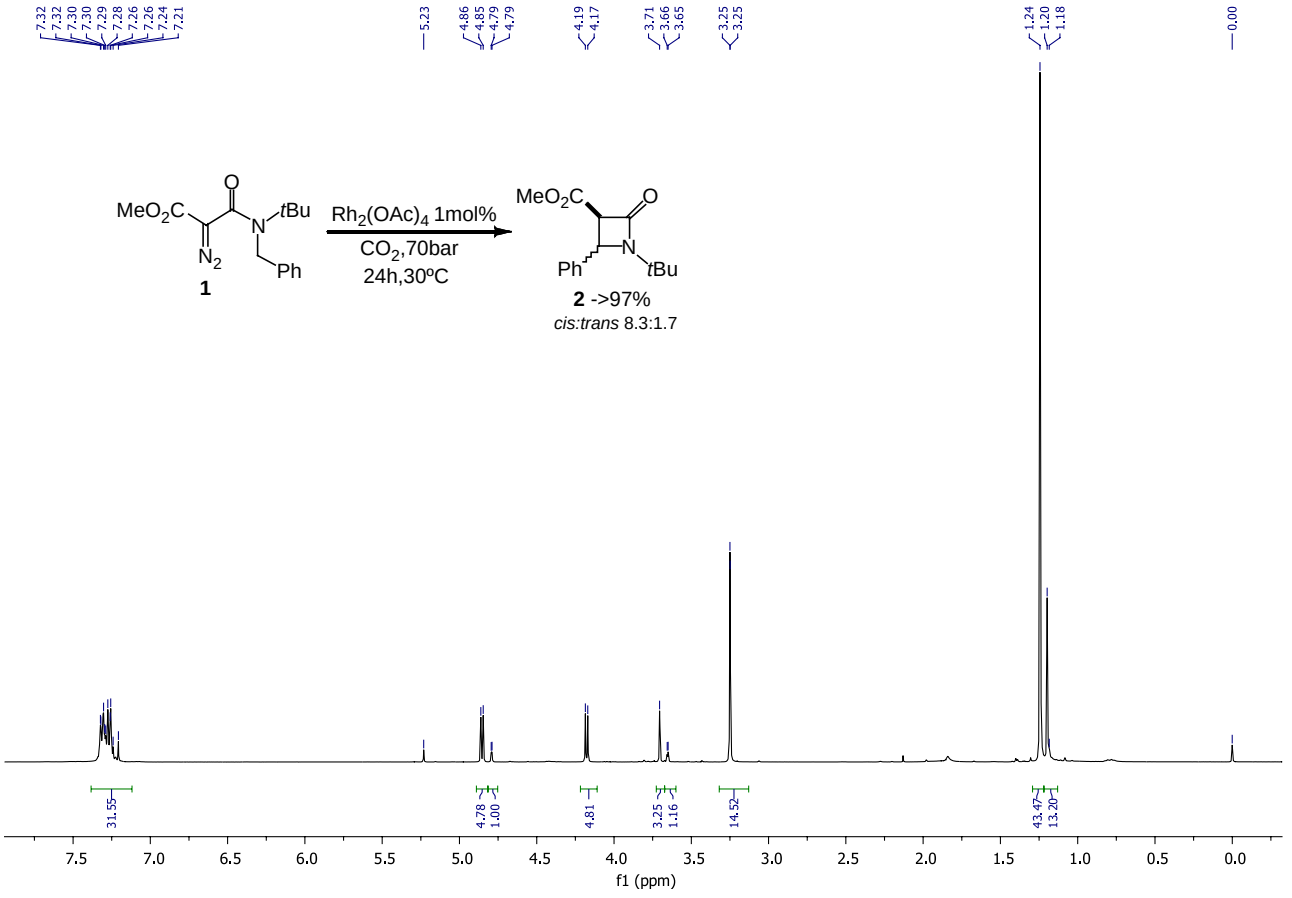

**Scheme S18**. – $^{31}$P NMR spectrum of crude cyclization reaction of 14.



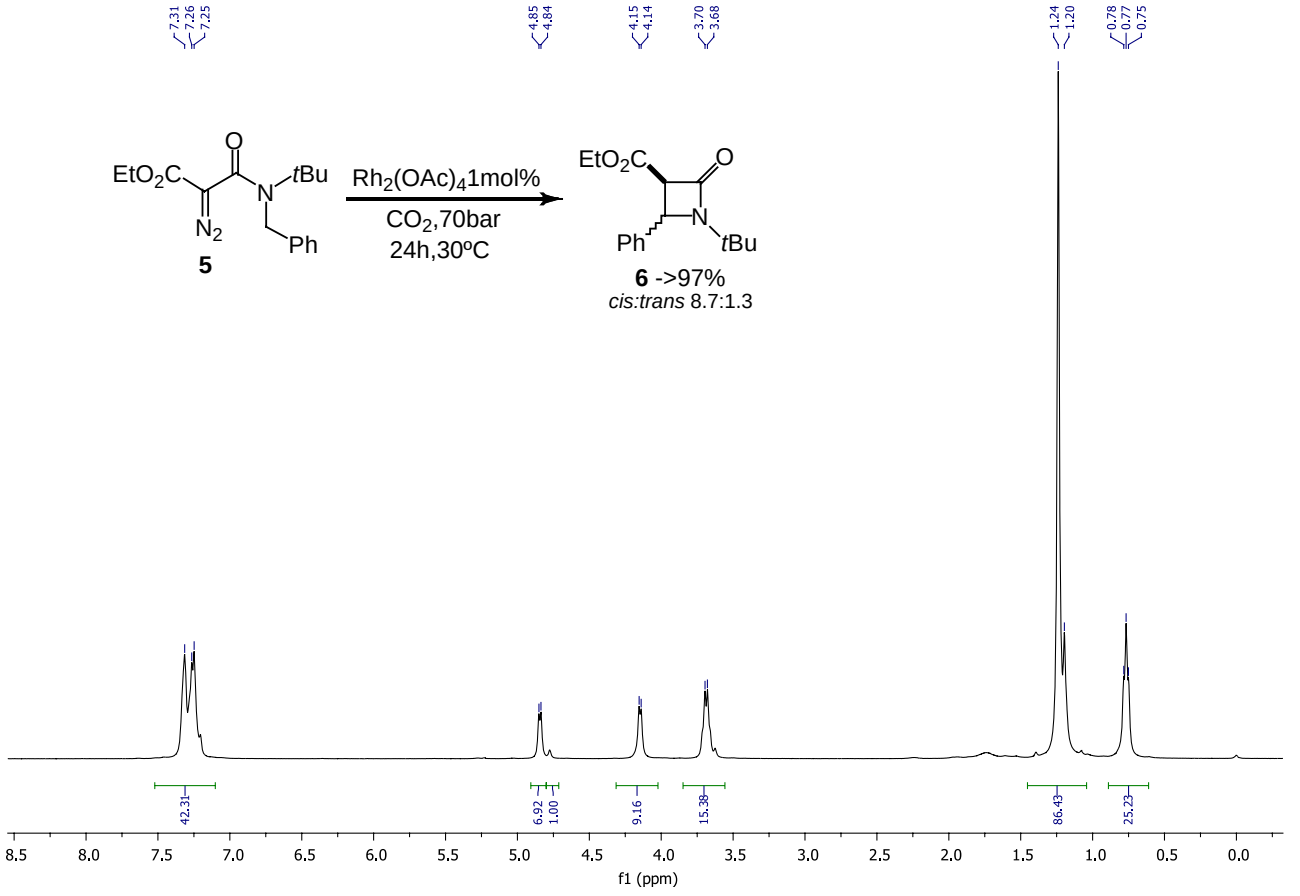

**Scheme S19**. – $^{1}$H NMR spectrum of crude cyclization reaction of 17.



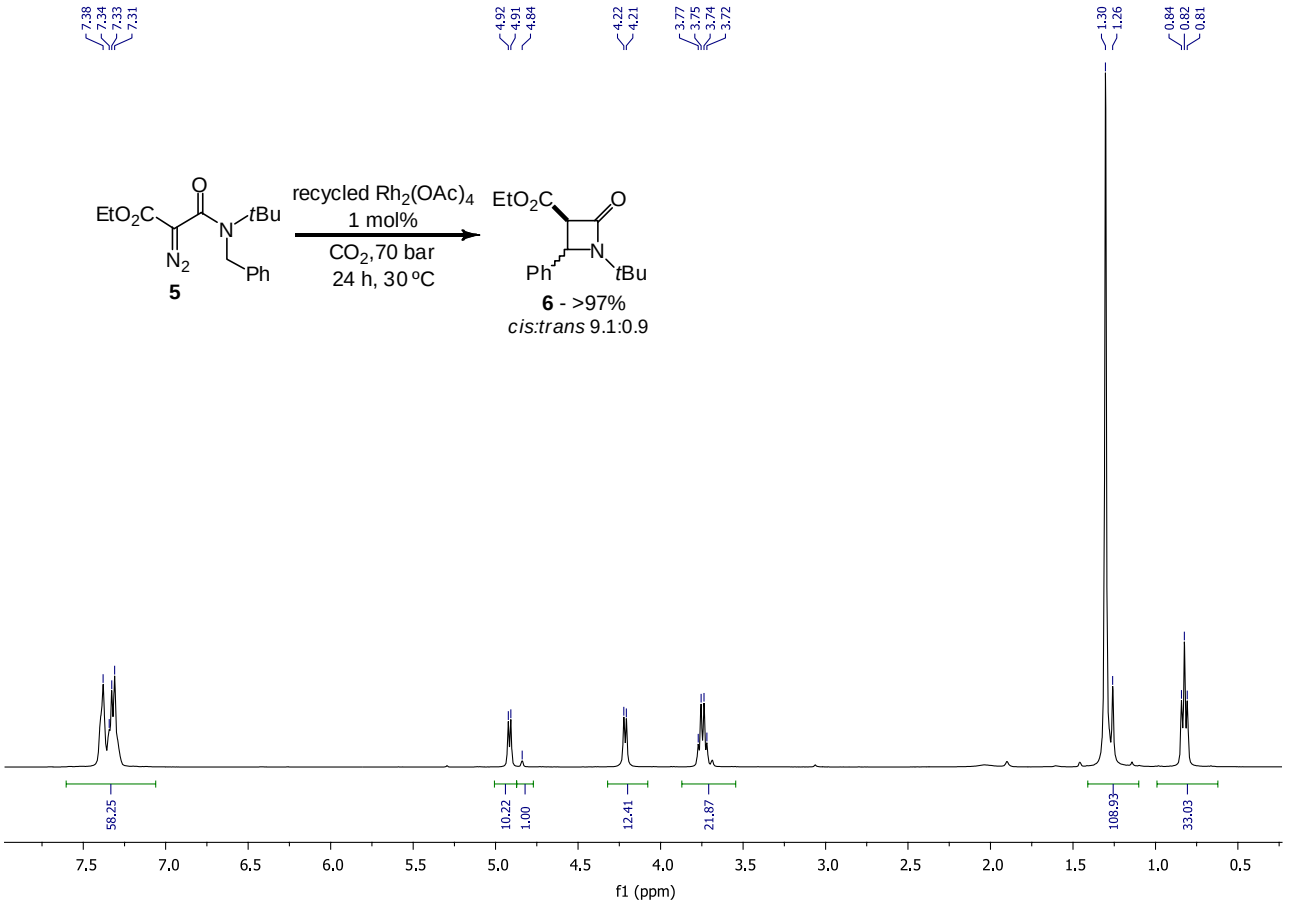

**Scheme S20**. – $^{31}$P NMR spectrum of crude cyclization reaction of 17.




**Scheme S21**. –$^{1}$H NMR spectrum of crude cyclization of 1 catalyzed by $Rh_2(OAc)_4$.




**Scheme S22**. $-^{1}$H NMR spectrum of crude cyclization of 5 catalyzed by $Rh_2(OAc)_4$.




**Scheme S23**. –$^{1}$H NMR spectrum of crude cyclization of 5 using recycled $Rh_2(OAc)_4$.