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Ruthenium (II) Catalyzed Ring Closure of Prochiral α-Chloro-N-Tosyl Amides: A Diastereoselectivity Study.

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Abstract: Prochiral N-tosyl amides cyclized under $(Ph_3P)_3RuCl_2$ catalysis gave diastereomeric 2-pyrrolidinone products. Stereoselectivity depended upon the size of C2-substitutents.

Nearly twenty years ago, Matsumoto[1] reported that $(Ph_3P)_3RuCl_2$ catalyzed the addition of α–chloro esters to alkenes. Since then Itoh,[2] Weinreb,[3] and Tseng[4] have led the development of this catalyst. Their studies identified substrates suitable for catalysis, found other transition metal catalysts, and showed that elaborate cyclic compounds can be prepared by this methodology. The current mechanistic understanding of this catalysis involves chlorine atom abstraction by the ruthenium catalyst, addition of the incipient carbon radical to the alkene, and chlorine atom delivery by the ruthenium (III) complex.[5] To obtain more information about this mechanism we have undertaken a study of the diastereoselective ring closure of alkyl-substituted N-tosyl amides with the goal of finding structural and reactivity characteristics of intermediates involved in this reaction.

Stork[6] and Padwa[7] both noted the benefit of a sulfonyl group on nitrogen in radical cyclization reactions. For this reason N-tosyl amides **1a-f** were selected for our study. Acylation of sodium allylsulfonamide with an appropriate acid chloride proceeded smoothly in 0.3 M THF solution giving the stable, white, crystalline amides in 69-37% yield (eq 1). Alkylation of dilithio-dichloroacetate with 2-bromopropane or benzylbromide[2a] gave the α,α–dichloroacids needed for **1d** and **1e**. The acid for **1f** came from an Ireland-Claisen rearrangement of 3-methyl-2-butenyl dichloroacetate.[8] The product from the rearrangement hydrogenated smoothly over Wilkinson's catalyst yielding 2,2-dichloro-3,3 -dimentylpentanoic acid in 50% yield after recrystallization.[9]

(1)

a: R= Cl, **b**: R= H, **c**: R= CH_3, **d**: R= iPr, **e**: R= CH_2Ph, **f**: R= t-Amyl ($C(CH_3)_2CH_2CH_3$)

Ruthenium (II) catalyzed cyclization of **1a-f** ran efficiently with 3 mol% of catalyst (0.006 M)[10] at 100 ° C providing mixtures of diastereomeric 2-pyrrolidinones and unreacted acylsulfonamides (eq 2) . No reduction, endo-cyclization, or telomerized products were observed.[11] Removal of the catalyst on a silica gel plug gave crude reaction mixtures from which the diastereomeric ratios were determined by ^1H NMR. The diastereotopic chloromethyl protons appeared in an ABX pattern between δ 3.00-4.07 in C_6D_6 and were used to measure the isomeric ratios. The isomeric pyrrolidinones were separated by chromatography and completely characterized.

All cyclized products showed carbonyl stretches between 1754-1741 cm^{-1} in the infrared and the C3 methine hydrogen appeared as an upfield multiplet. These spectral features established the 2-pyrrolidinone structure.

NOE difference spectroscopy[12] was initially used for stereochemical assignment. For cis isomers, a positive NOE between a resonance on the alkyl side chain and the C3 hydrogen was observed (See Figure 1 and Table 1.). For example, irradiation of the methyl singlet (δ 1.08) in cis 2c gave a 4.7% enhancement of the tertiary proton signal. A smaller enhancement (3-6 %) was also seen for the syn proton at C4. In contrast, no NOE between the alkyl side chain and the C3 hydrogen was seen for the trans isomers. Phenomenologically, the chemical shift of the C3 proton became a sensitive indicator of stereochemistry. In all cases, the proton signal at C3 in the cis isomer appeared downfield relative to the signal in the trans isomer. This observation can be rationalized by considering the gauche arrangement of the chlorine atom at C2 and the hydrogen at C3 in the trans isomer. The magnetic field of the proximal electronegative atom shifts the proton resonance to higher field. This fortuitous observation should be valuable when reliable NOE measurements are not available.

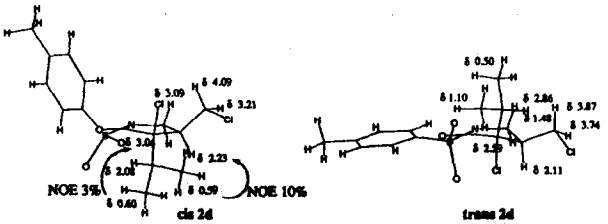
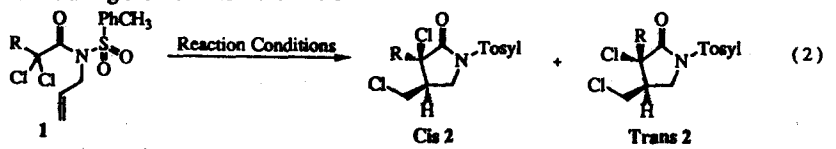


Figure 1. Spectral and NOE Difference Data for cis 2d and trans 2d. Structures based on molecular mechanics calculations using the AMBER force field.



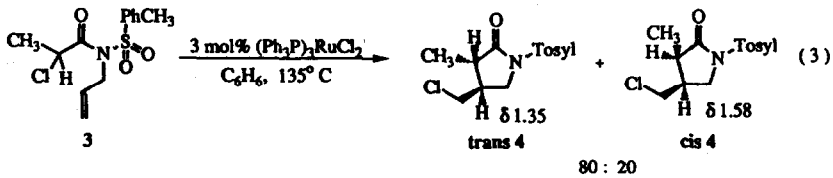
(2)

Table 1. Diastereoselectivity of $(Ph_3P)_3Ru\ Cl_2$ Catalyzed Cyclization.

α-Chloro N-tosyl Amide	R	Reaction Conditions	NMR Diastereomer Ratio cis-2 : trans-2	Isolated Total Yield %	Methine C-H δ *Cis:Trans* (% NOE)[a]
1a	Cl	A	---	63	1.97
1b	H	B	22 : 78	65	1.64 : 1.4
1c	CH_3	A	27 : 73	69	2.08 : 1.48 (4.7)[b]
1d	iPr	A	77 : 23	54	2.22 : 2.15 (10.0)[c]
1e	CH_2Ph	A	95 : 5	57	2.18 : 1.37 (7.2)[d]
1f	t-Amyl	A	>100 : 1	70	2.47 (6.4 [e], 6.2)[f]

Reaction Conditions: A: 0.12 M N-tosyl amide, 0.005 M $(Ph_3P)_3RuCl_2$, 100° C, 4h in benzene. B: As in A except heating to 135° C. [a] NOE difference spectroscopy for cis-isomer only. [b] Irradiation at 1.08(s). [c] Irradiation at 0.61(two d). [d] Irradiation at 3.34(d). [e] Irradiation at 0.72(s). [f] Irradiation at 0.83(s).

The results of our diastereoselectivity study are summarized in Table 1. A generally smooth transition from predominant trans selectivity to cis selectivity occurred as R increased in size from hydrogen to t-amyl. With very large alkyl substituents no trans isomer was observed. The dominant diastereomer (except in the case of **1c**, R= CH_3) positioned the largest substituent at C2 trans to the chloromethyl group. Subsequent studies with **cis** and **trans 2b** and **2d** showed that these materials do not isomerize (<5%) under the conditions of ruthenium catalyzed cyclization.[13] From this information we concluded that the observed diastereoselectivities are kinetically controlled. The unexpected result with **1c**, on the other hand, suggested that **2c** equilibrated rapidly to a thermodynamic mixture under the reaction conditions. To exclude the possibility of isomerization we prepared the monochloro N-acylsulfonamide **3**. This substrate cyclized at 135° C giving two diastereomeric 2-pyrrolidinones in 56% yield (eq 3). The expected trans isomer predominated in a 80 : 20 ratio. The chemical shift method for assigning stereochemistry similar to that used with **2** could not be applied to **4** because no chlorine was present at C2. However, a 9.6% NOE enhancement of the C3 proton in **trans 4** was observed upon irradiation of the methyl doublet at δ 0.61. Cyclization of **3** followed the trend observed with **1d-f** in that the two groups with the largest A values at C2 and C3 assumed trans substitution on the pyrrolidinone ring. Note that only the isomeric designation changed in going from **2** to **4**; the diastereoselectivity remained the same.



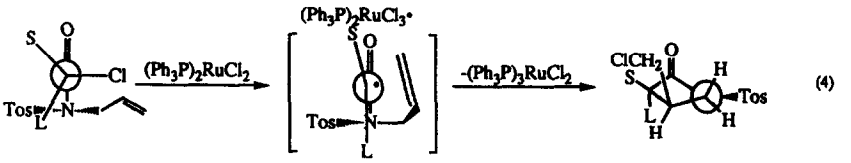
3 → **trans 4** + **cis 4** (3)

80 : 20

Discussion: Chlorinated N-tosyl amides are important substrates for the study of ruthenium (II) catalyzed cyclizations. Reliable diastereoselectivity data is obtained from substrates **2** and **3** because competing reduction, endo-cyclization, and telomerization reactions do not occur. The kinetic diastereoselectivity of these cyclizations positions the largest substituent at C2 trans to the chloromethyl group. Ikeda[14] found similar trans diastereoselectivity in the Bu_3SnH mediated cyclization of monochloroamides. It is important to note however that the stereoselectivity for N-tosyl amide cyclizations parallels the thermodynamic stabilities of the isomeric 2-pyrrolidinones.[13] Therefore a significant amount of ring strain, torsional strain, and steric interactions in the pyrrolidinone products must be present at the transition state. Inspection of the two isomeric pyrrolidinones reveals significant features of the transition state.

Molecular mechanics, using AMBER, calculates that **cis 2d** is more stable than **trans 2d** by 0.8 kcal. The disposition of the tosyl group relative to the pyrrolidinone ring and the conformation of the rings themselves are qualitatively similar (See Figure 1.). Both pyrrolidinone rings are nearly flat, although the trans isomer displaces the C3 carbon approximately 0.2 Å out of the plane defined by the N-C1-C2-C4 atoms. The similarity of the two pyrrolidinone rings suggests that similar chair-like transition states lead to each isomer. This analysis requires that the stereoselection in N-tosyl amide cyclization be controlled by the conformational preference of the α–acyl radical intermediate (eq 4). In the α–acyl radical intermediate, the largest group at the radical center is directed away from the carbonyl oxygen. Although this conformation is usually less stable, with N-tosyl amides this may not be the case. We have obtained two crystal structures on chlorinated N-tosyl amides and each shows that the nitrogen is planar and that the lone pair on nitrogen is extensively delocalized towards the sulfonyl group As a result, nitrogen can position its substituents 90 ° to the O1-C1-C2 plane. This reduces steric interactions

and directs the allyl group in a position suitable for cyclization. A second feature which may contribute to the conformation of the α–acyl radical is association of the ruthenium (III) complex with the carbonyl oxygen. The ruthenium complex can not effectively move away from the C2 carbon because the tosyl group blocks an adjacent region. We are currently conducting experiments to test this hypothesis.



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