THE MECHANISM OF CONFIGURATION RETENTION IN THE SUBSTITUTION REACTION OF C4-TOSYLOXYPROLINE WITH LITHIUM DIARYLCUPRATE†

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Abstract-The mechanism of configuration retention during the substitution reaction of C4-tosyloxyproline with lithium diarylcuprate was studied. Among the three possible intermediates (**a**~**c**), **c** has been found to be the origin of the retention mechanism.

4-Hydroxyproline is a useful starting material for the syntheses of alkaloids, and chiral ligands which are often synthesized by the substitution reaction of their C4-tosylate.[1] In 1986 Thottathil and Moniot reported an interesting substitution reaction of 4-tosyloxyproline with lithium diphenylcuprate.[2] The reaction of both the trans-and cis-4-tosyloxyprolines (**1** and **4**) gave two substituted products, the cis- and trans-4-phenylproline derivatives, whose configuration at C4 is always retained and at C2 is epimerized (Figure 1). The absolute configuration of **2** was determined by X-ray crystallography after conversion to **7**. The cis-isomer (**3**) was produced by epimerization at C2 of **2** , which was confirmed by treatment of **2** with Ph_2CuLi or LDA to produce **2** and **3** in a ratio of 2:1. During the substitution reaction, the product ratio depends on the protective groups of the amine and the carboxyl, the configuration of the substrate, and the reaction conditions. We employed this reaction for the synthesis of acromelic acid analogs.[3] In connection with this work, we studied the origin of the retention of the C4-configuration.

† Dedicated to the memory of the late Prof. Yoshio Ban.
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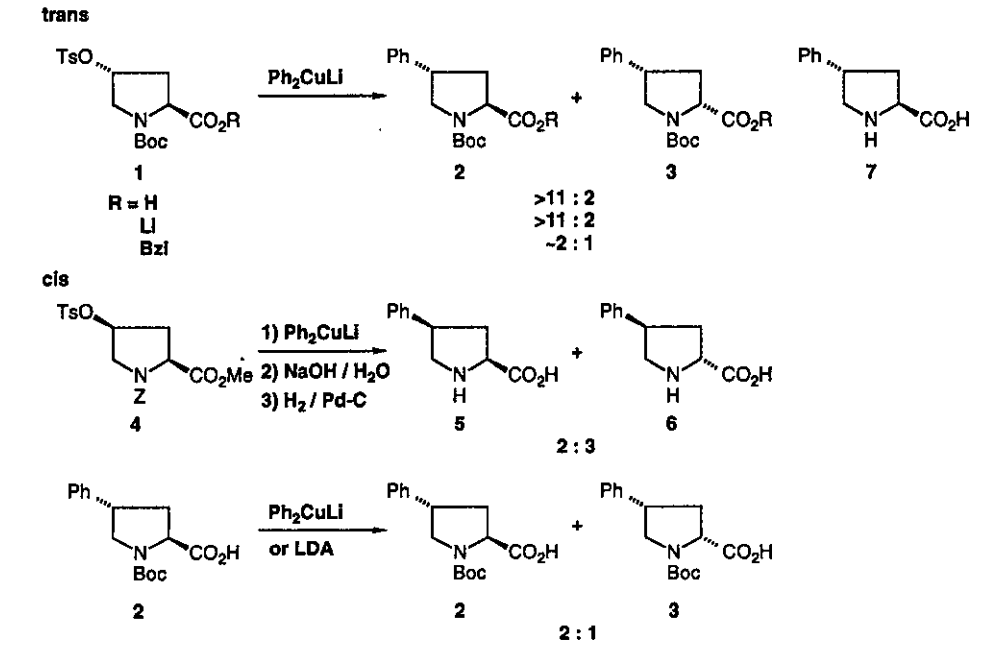
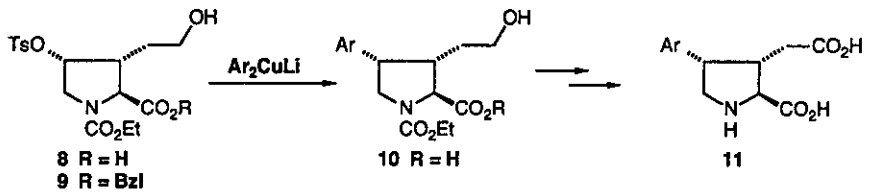
Figure 1



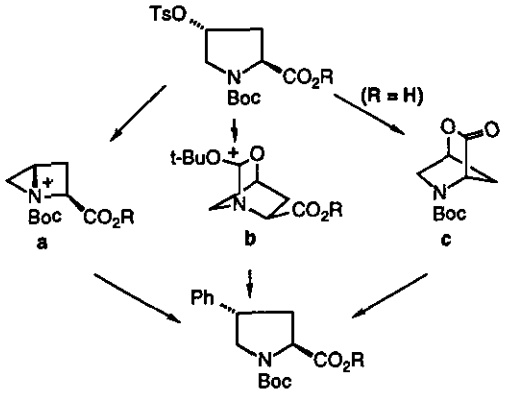
The substitution reaction of the carboxylic acid (**8**), an intermediate for the synthesis of acromelic acid analogs, smoothly proceeded to give a sole product (**10**) with the right stereochemistry. On the other hand, the corresponding reaction of the benzyl ester (**9**) gave a complex mixture (Figure 2). In the former case, the configuration of C2 was not affected, which was probably due to the steric effect of the C3-substituent. To clarify the mechanism, many other derivatives of 4-tosyloxyproline and of 3-tosyloxypiperidine were exposed to the same substitution reaction, but limited compounds (**1** (R=H) and **8**) gave the desired product with retention of configuration at C4, while others gave inversion products at C4.[4] Only the substrates which have a free carboxylic acid at C2 produced the retention product at C4.

Figure 2



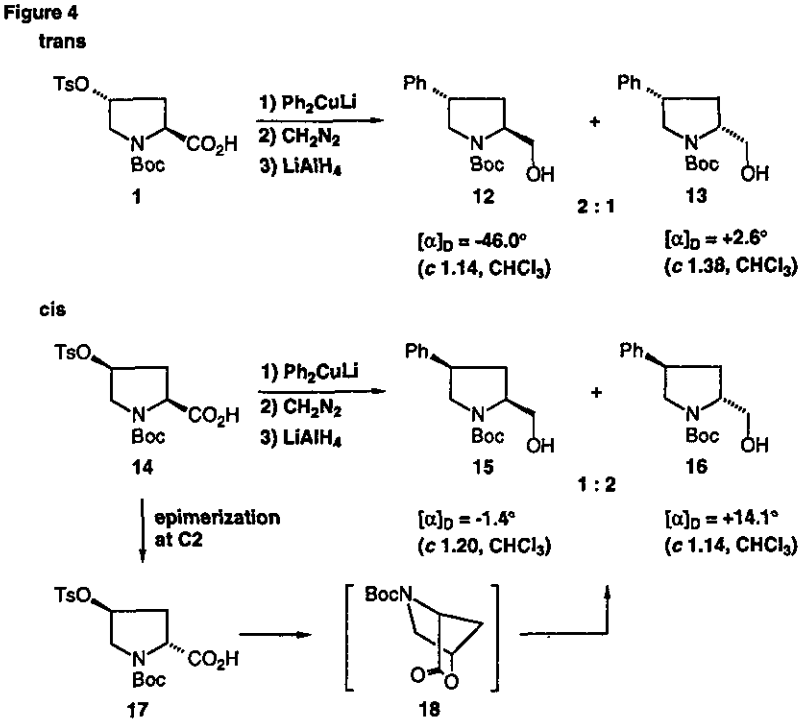
Thottathil and Moniot assumed this substitution reaction took place by two succesive inversion processes in which the first step is the formation of an activated bicyclic intermediate (**a** or **b** or their equivalent) by an inversion process which is ring-opened by the reagent in the second inversion process (Figure 3).[5] However, our results indicate the participation of the carboxylic acid group (**c**). If the intermediate is **c**, only the trans-

Figure 3



isomer will afford the desired retention product at C4. Accodingly, the cis-isomer (**14**) [6(a)] was tested under the same conditions and the resulting data were compared with those of the trans-isomer (**1**) (Figure 4).[6(b)] Since the substituted products, the trans- and cis-isomers, were not separable on a silica gel column, after conversion to alcohols, they were separated by preparative silica gel tlc. The trans-tosylate (**1**) gave the trans- and cis-substituted products (**12** and **13**)[7] in a ratio of 2:1, respectively. Under the same conditions, the corresponding cis-tosylate (**14**) also afforded the trans- and cis- substituted products in the same ratio as in the trans-one. Comparing the optical rotations between the trans-isomers (**12**) and (**16**), the optical purity of **16** is lower than that of **12**. Also **12** and **16** showed rotations with opposite signs, which indicate that the reaction of the cis-

Figure 4



isomer (**14**) proceeds through two processes involving inversion and retention at C4, and the latter process is much faster than the former one. Optical rotations of cis-isomers (**13**) and (**15**) also showed the same tendency.

Considering these results, the formation of the **15** and **16** from the cis-tosylate (**14**) can be explained by scrambling the two processes; one is a direct inversion at C4 with the reagent, and the other is successive epimerization at C2, lactone formation, and substitution at C4 with totally retention of the C4-configuration. Under the conditions of the substitution reaction, the lactone formation of **1** would be much faster than direct substitution at C4 and epimerization at C2. The faster lactone formation would have prevented the racemization at C2 of **1** (the enolate of the lactone is an anti-Bredt's compound), which consequently leads to perfect retention at C4. Finally, it is concluded that this substitution reaction proceeds through intermediate **c**, which has characteristics of trans-tosyloxyproline, to produce the retention product at C4.

REFERENCES

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2. J. K. Thottathil and J. L. Moniot, *Tetrahedron Lett.*, 1986, **27**, 151.
3. K. Hashimoto and H. Shirahama, *Tetrahedron Lett.*, 1991, **32**, 2625.
4. Unpublished results.
5. Participation of double bond in the substitution reaction of tosylate with organocuprate is reported : G. H. Posner and J.-S. Ting, *Tetrahedron Lett.*, 1974, 683.
6. (a) The cis-isomer (**14**) was prepared according to the following papers: M. M. Bowers-Nemia and M. M. Joullié, *Heterocycles*, 1983, **20**, 817. A. A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, 1957, **79**, 185. (b) The trans-isomer (**1**) was prepared according to the reference 2.
7. ^{1}HNmr (400MHz, $CDCl_3$) for **12**: δ (ppm) 1.47(9H, s), 2.03(1H, m), 2.17(1H, dt, *J*=12.5, 8.0Hz), 3.35-3.54(2H, m), 3.65-3.83(3H, m), 4.20(1H, m), 4.34(1H, brs), 7.20-7.35(5H, m).
13: δ 1.49(9H, s), 1.67(1H, q, *J*=10.7Hz), 2.41(1H, dt, *J*=10.7, 5.3Hz), 3.20-3.30(2H, m), 3.68(1H, ddd, *J*=1.3, 8.0, 12.0Hz), 3.76(1H, t, *J*=12.0Hz), 3.99(1H, m), 4.09(1H, dddd, *J*=5.3, 8.0, 10.7, 12.0Hz), 5.29(1H, dd, *J*=1.3, 12.0Hz), 7.21-7.36(5H, m).

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