Supplementary Information

2-Pyrrolidinones and 3-Pyrrolin-2-ones: A Study on the Chemical Reactivity of These Structural Moieties

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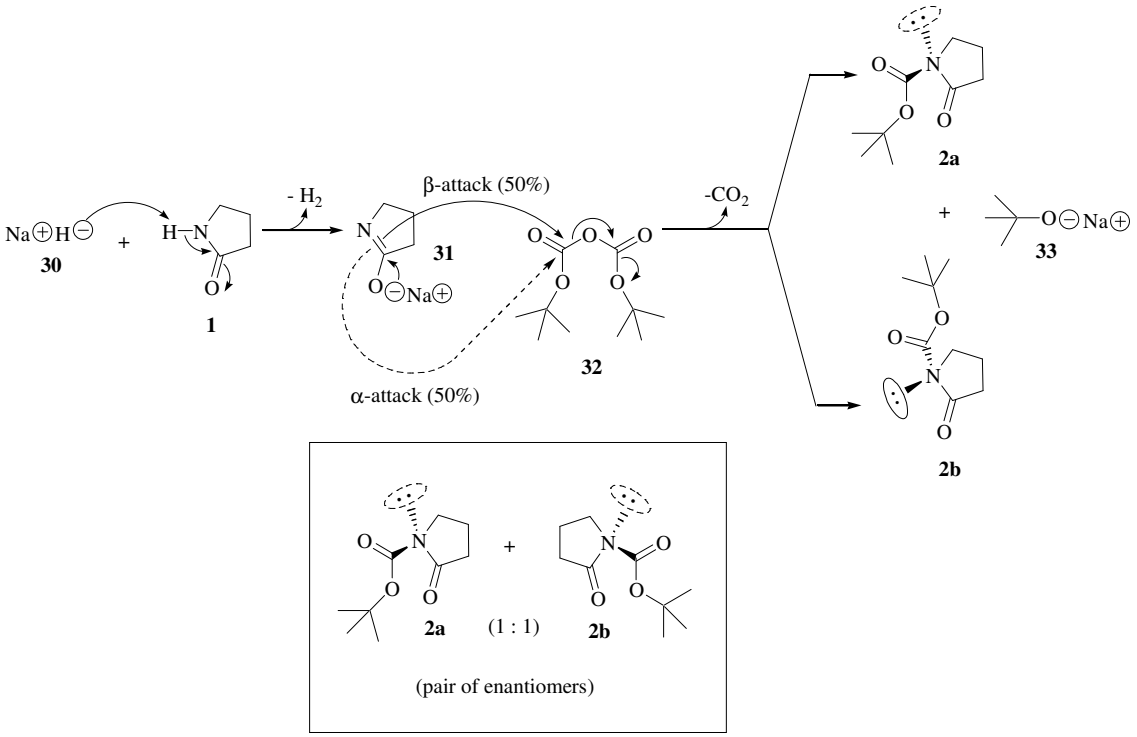
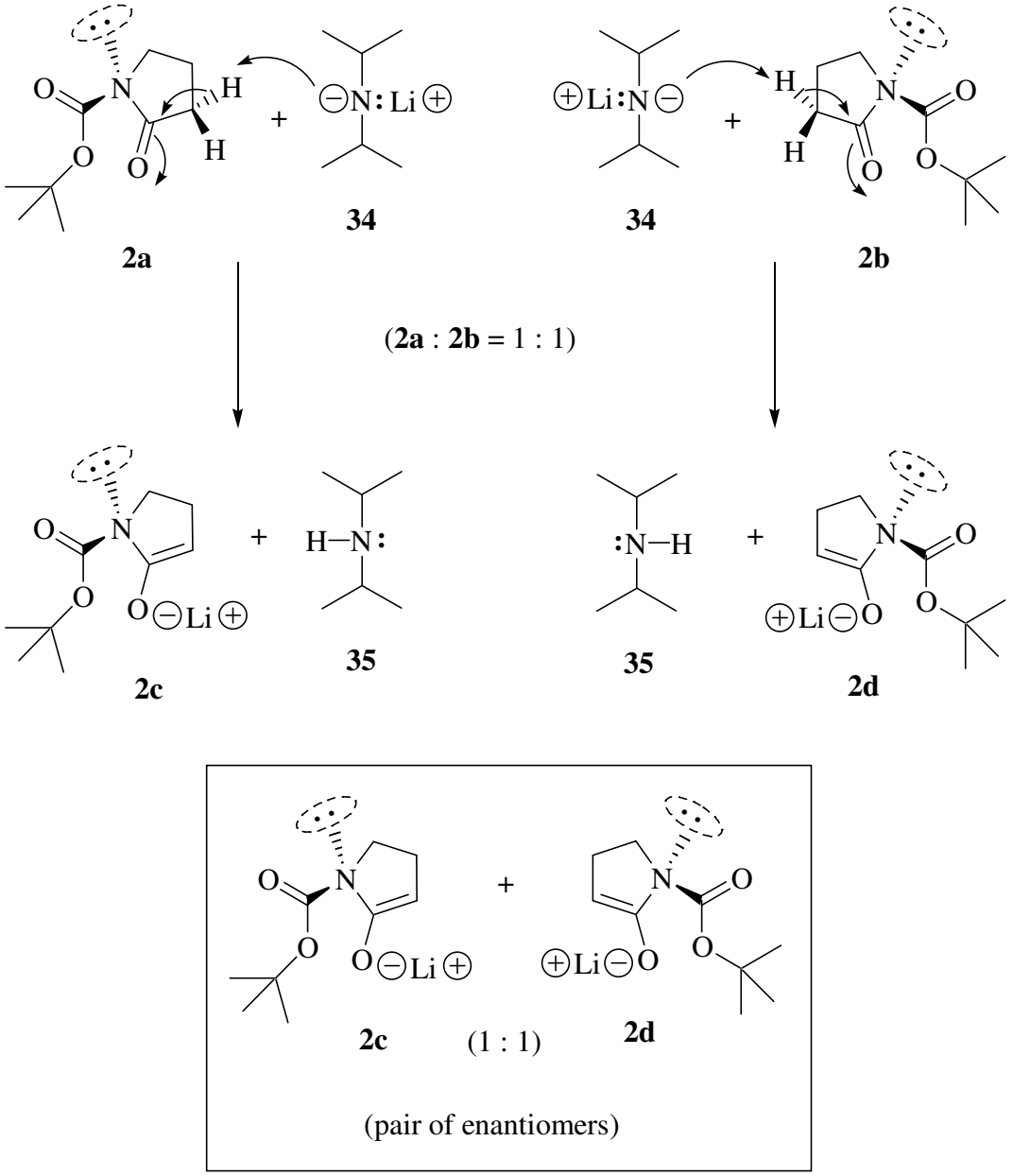
Table of Contents

This supplementary material displays the speculative mechanisms for the reactions presented in the text of the paper. The stereochemical aspects of the reactions are being considered for a better understanding of the stages involved in the described chemical transformations.

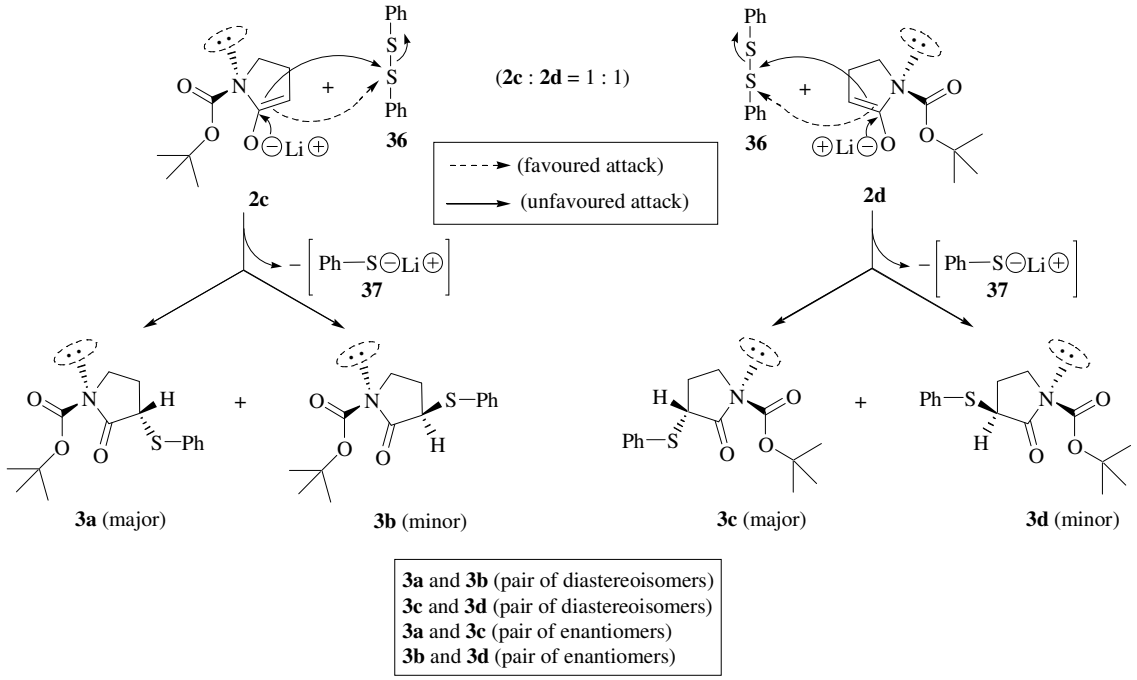


Scheme S1. Speculative mechanism for the synthesis of the isomers **2**.

In the main text of the paper we just referred to a isomer relative to the pairs of enantiomers derived from 2-pyrrolidinones and 3-pyrrolin-2-ones. In the usual conditions in which the NMR experiments are performed, without the use of shift reagents, the pairs of enantiomers are not differentiated by that technique of analysis. The isomers that are distinguished by NMR refers to the pairs of diastereoisomers. In the text of this supplementary material (Schemes S1, S5 and S12) we are considering similar the probability of attack for both α and β faces of the enolates, yielding a pair of enantiomers in equal molar quantities.

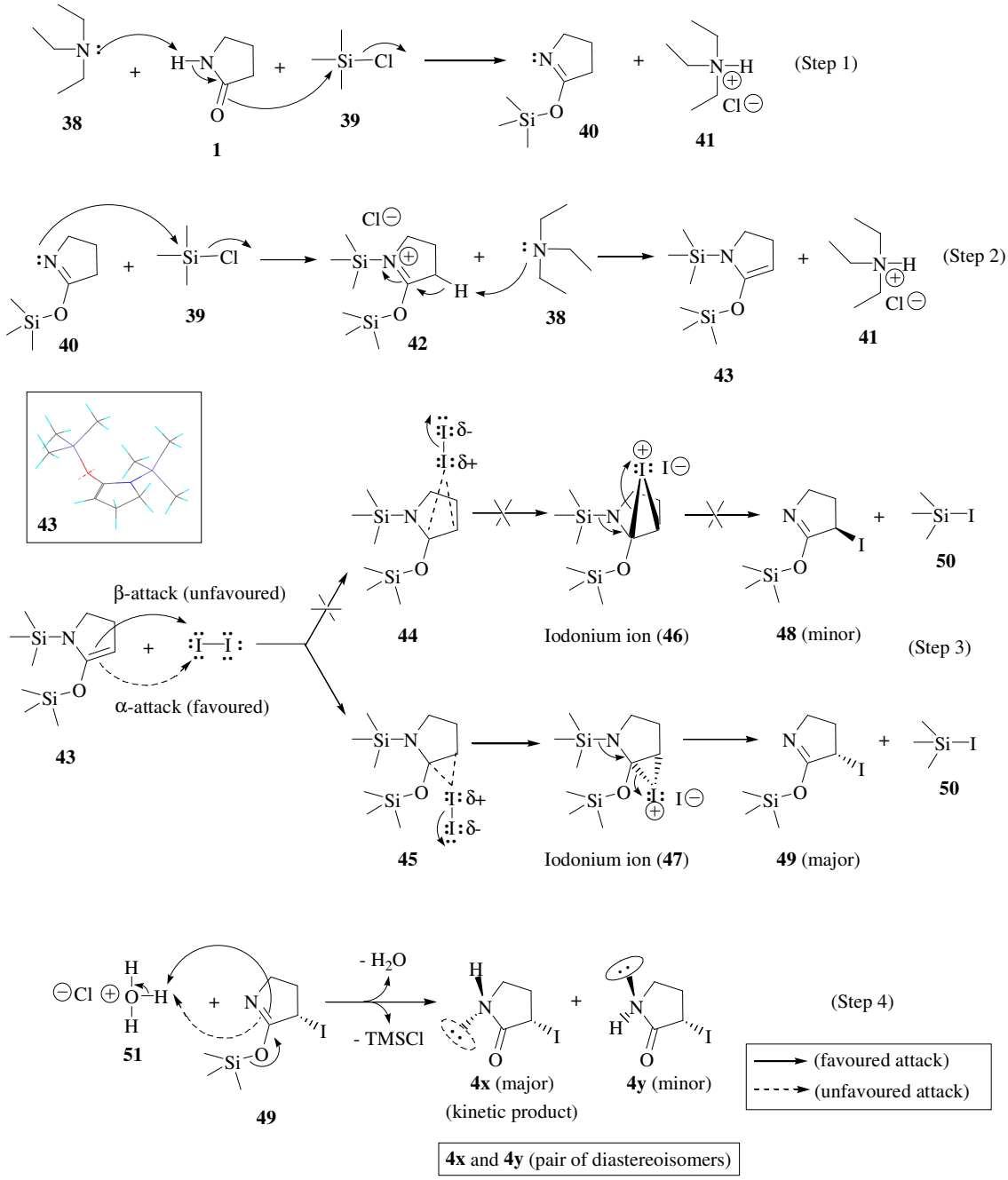


Scheme S2. Speculative mechanism for the synthesis of the pair of Lithium enolates **2c**-**d**.



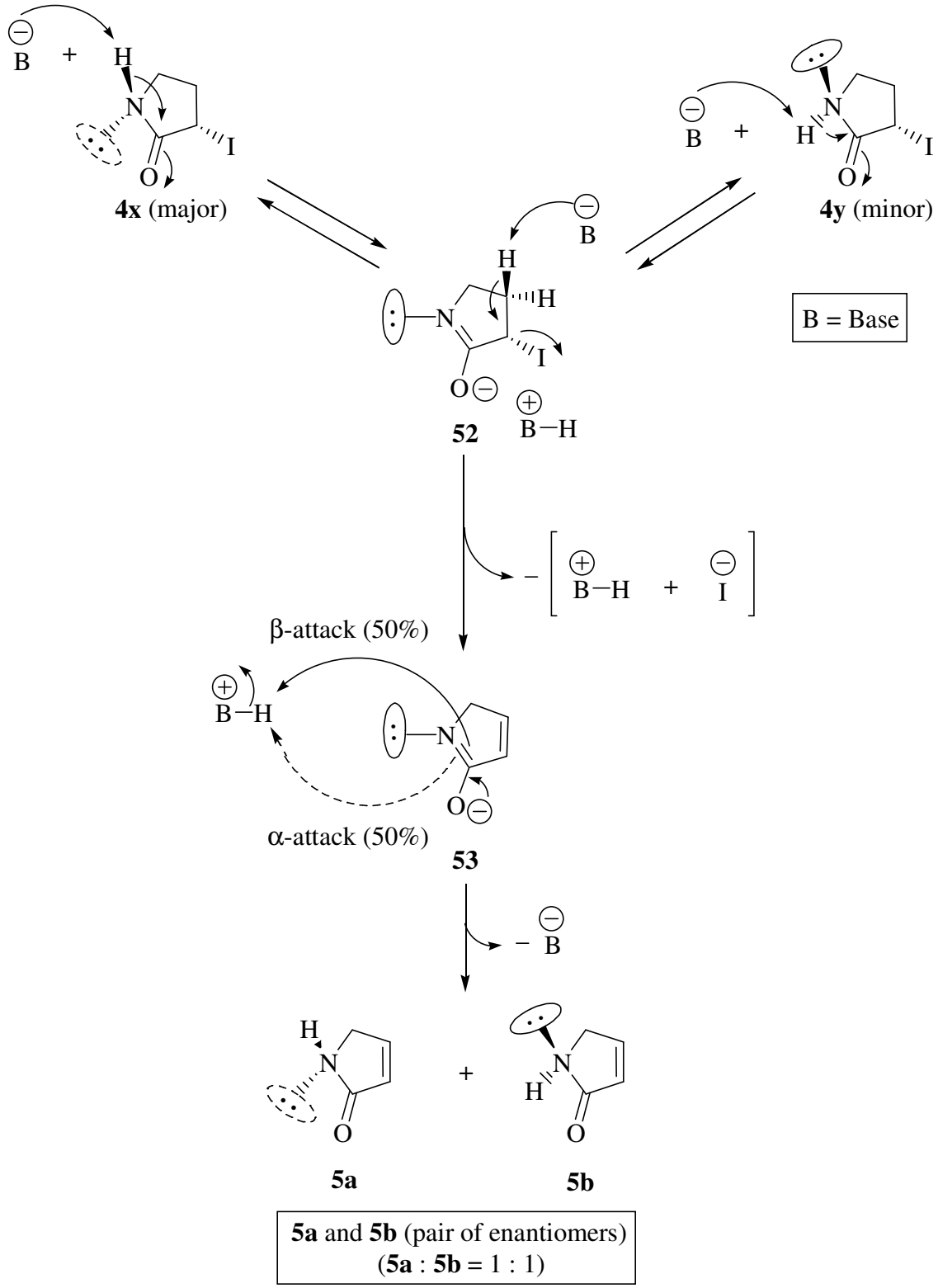
Scheme S3. Speculative mechanism for the synthesis of the isomers **3**.

We are considering, in the text of this supplementary material, the favoured attack of the enolate for the less hindered face opposed to the bulky groups.

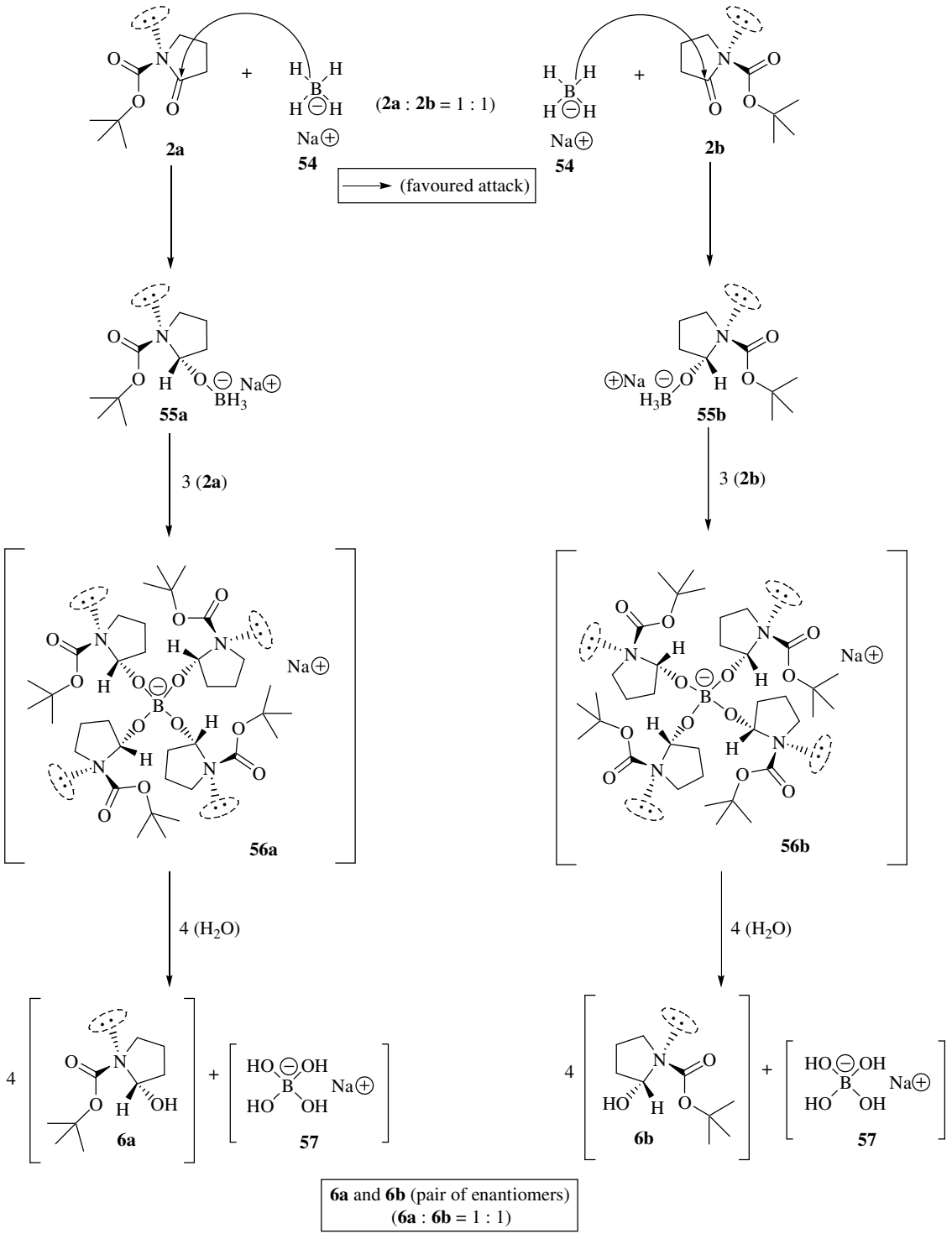


Scheme S4. Speculative mechanism for the synthesis of 3-iodine-2-pyrrolidinone (**4**).

We are considering, in Scheme S4, the exclusive formation of the iodonium ion **47** because the β face of the enolate **43** is highly hindered by the bulky group $OSiMe_3$, as shown by the three-dimensional structure inside of the square.

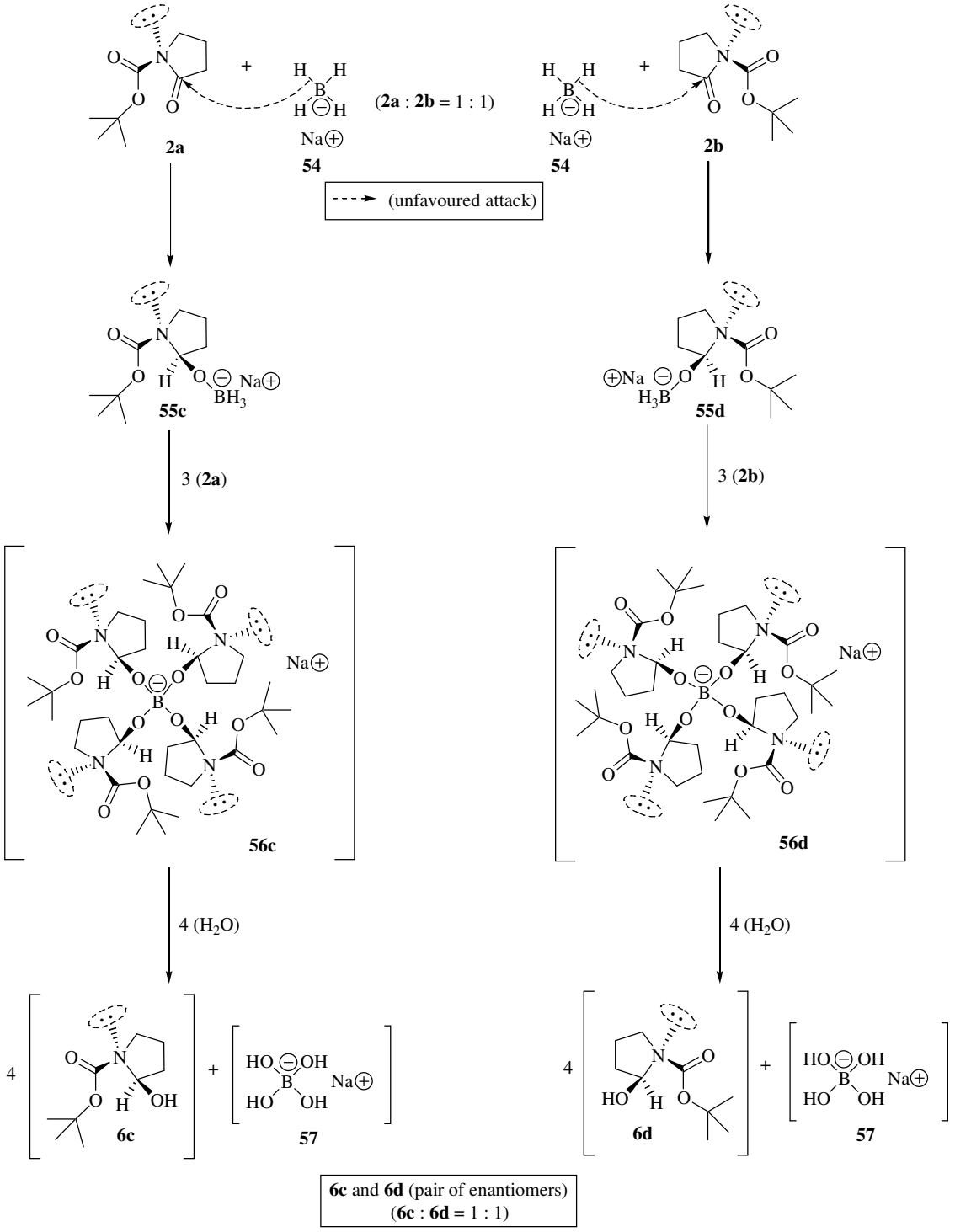


Scheme S5. Speculative mechanism for the elimination reaction of HI on 3-iodine-2-pyrrolidinone (**4**).

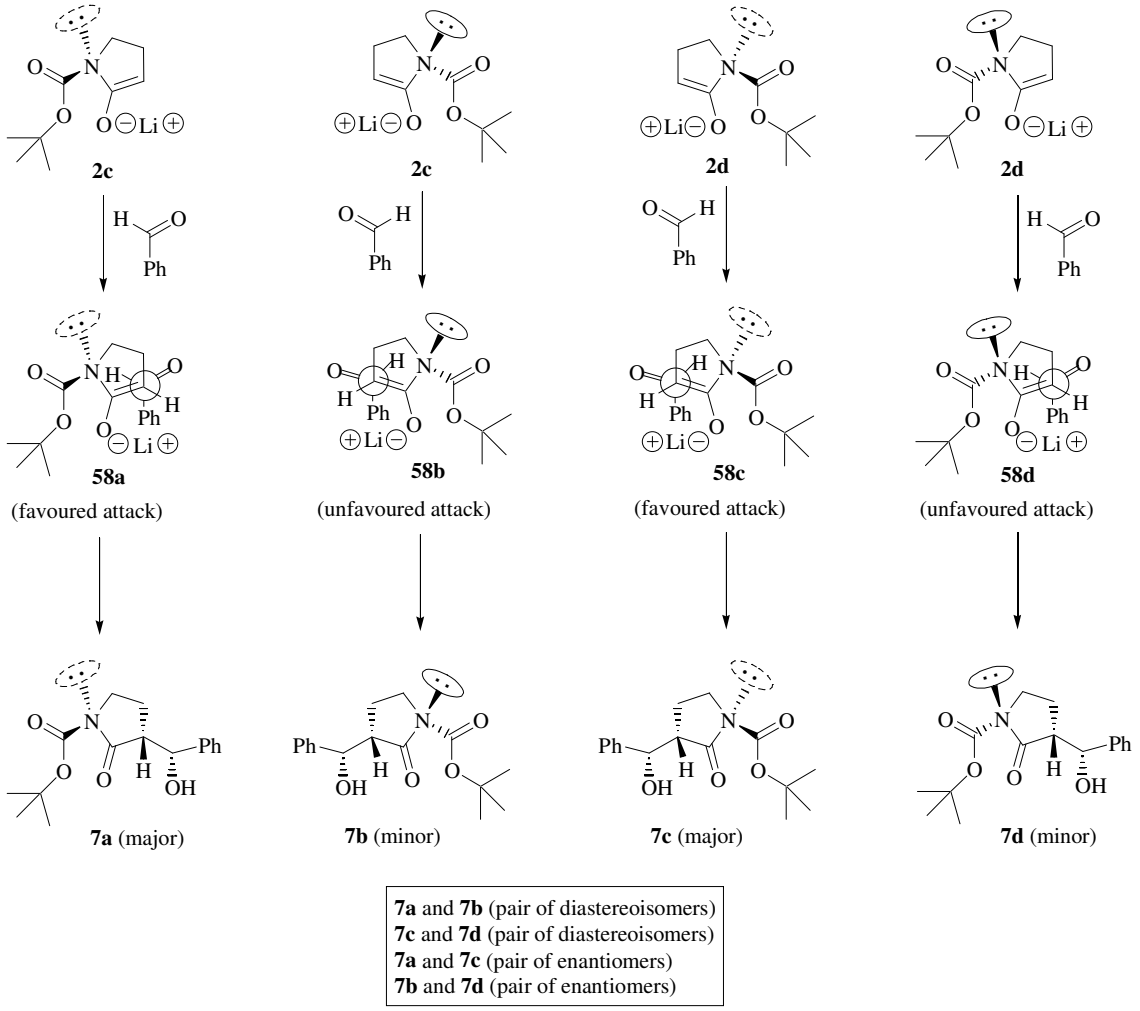


Scheme S6. Speculative mechanism for the synthesis of the hemiaminal **6**. Probable major isomers (**6a**-**b**).

We are considering, in Scheme S6, the favoured attack of hydride for the β face of the carbamate to furnish the intermediates **56a**-**b**, with less steric interactions than the intermediates **56c**-**d** shown in Scheme S7.

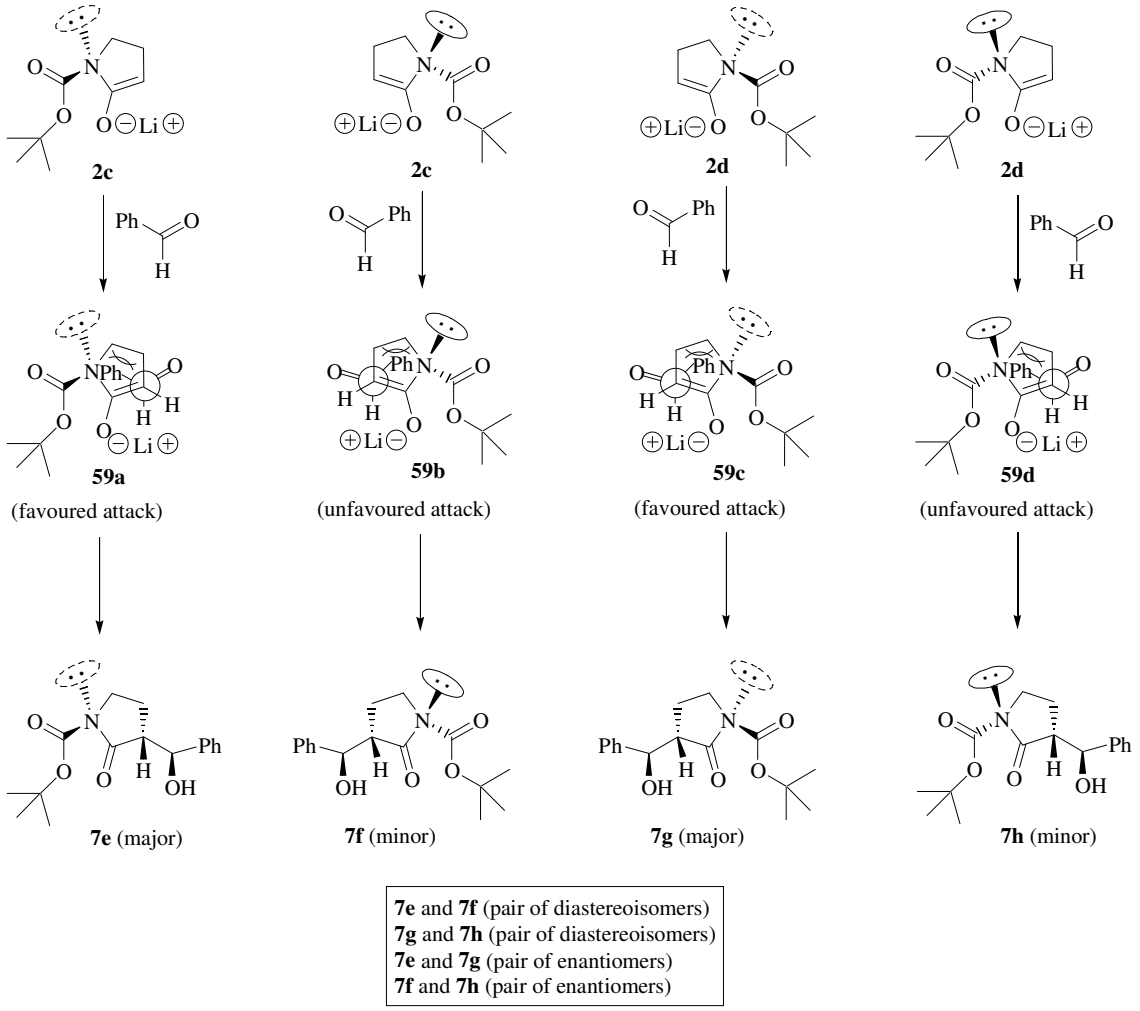


Scheme S7. Speculative mechanism for the synthesis of the hemiaminal **6**. Probable minor isomers (**6c**-**d**).



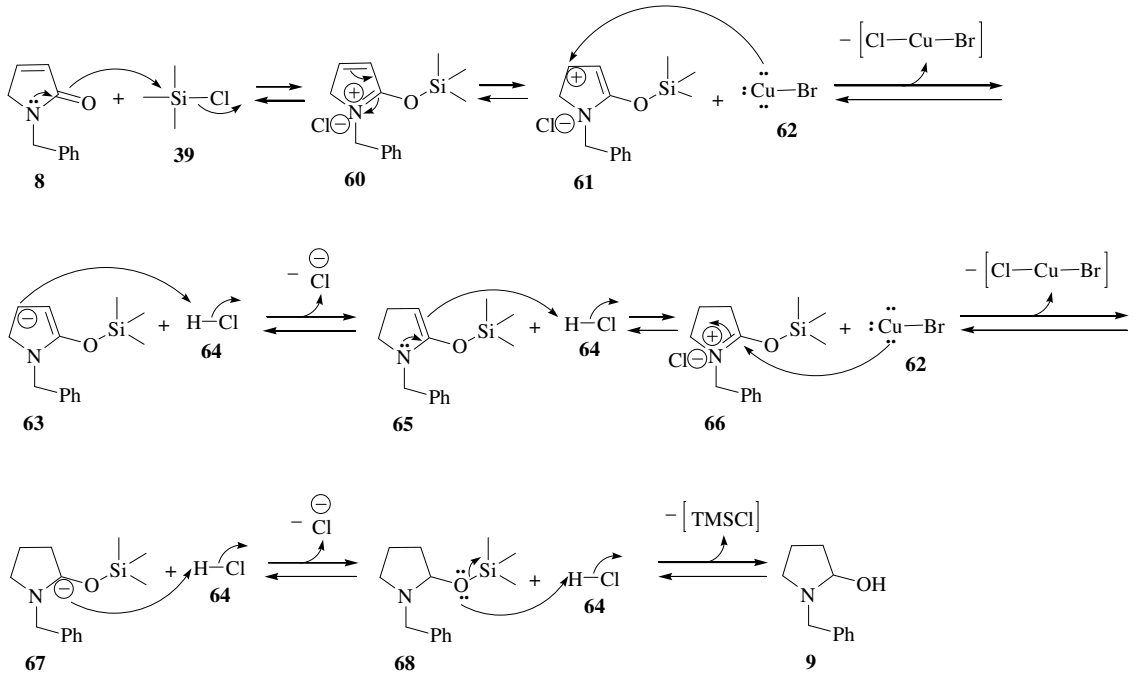
Scheme S8. Speculative mechanism for the synthesis of the majority *anti*-adducts **7**.

Superposed multiplets were detected at the ^{1}H NMR spectrum of **7**, and attributed to 2 *anti*-adducts. A major signal centralized at δ 3.28 (altered by D_2O) was assigned to methinic hydrogen attached to alkoxy carbon of the majority *anti*-adduct **7a/7c**, and a multiplet at δ 3.32-3.23 (altered by D_2O) was attributed to the same methinic hydrogen of the minority *anti*-adduct **7b/7d**. A broad singlet at δ 7.23 (D_2O exchange) was assigned to hydrogen of hydroxyl (deshielded by benzene ring) of the majority *anti*-adduct **7a/7c**. The signal attributed to this same hydrogen of hydroxyl of the minority *anti*-adduct **7b/7d** was detected at δ 7.25-7.20 (m, D_2O exchange). The proportion of the mixture of majority *anti*-adducts **7** (Scheme S8) in relation to the mixture of minority *syn*-adducts **7** (Scheme S9) is (3:1). This proportion was measured by integrals relative to signals of the methinic hydrogens, attached to alkoxy carbon, at the ^{1}H NMR spectrum.



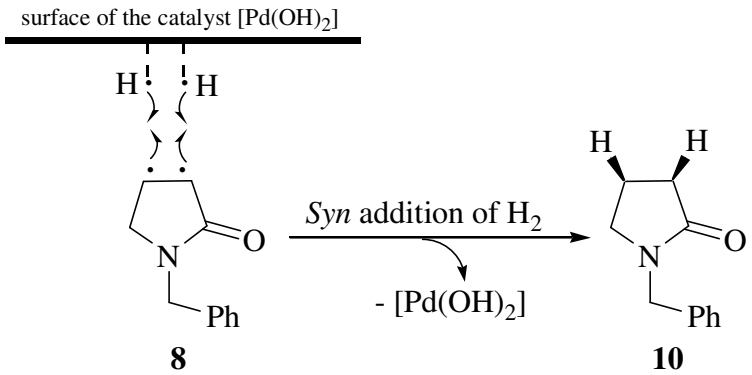
Scheme S9. Speculative mechanism for the synthesis of the minority *syn*-adducts **7**.

Signals were detected at the ^{1}H NMR spectrum of **7**, and attributed to 2 *syn*-adducts. A minor broad doublet at δ 4.83 (*J* 7.5 Hz) was assigned to methinic hydrogen attached to alkoxy carbon of the minority *syn*-adduct **7f /7h**, and a doublet at δ 4.72 (*J* 9.6 Hz) was attributed to the same methinic hydrogen of the majority *syn*-adduct **7e/7g**. A broad singlet at δ 6.80 (D_2O exchange) was assigned to hydrogen of hydroxyl (deshielded by benzene ring) of the majority *syn*-adduct **7e/7g**. The signal attributed to this same hydrogen of hydroxyl of the minority *syn*-adduct **7f /7h** was detected at δ 6.60 (bs, D_2O exchange).

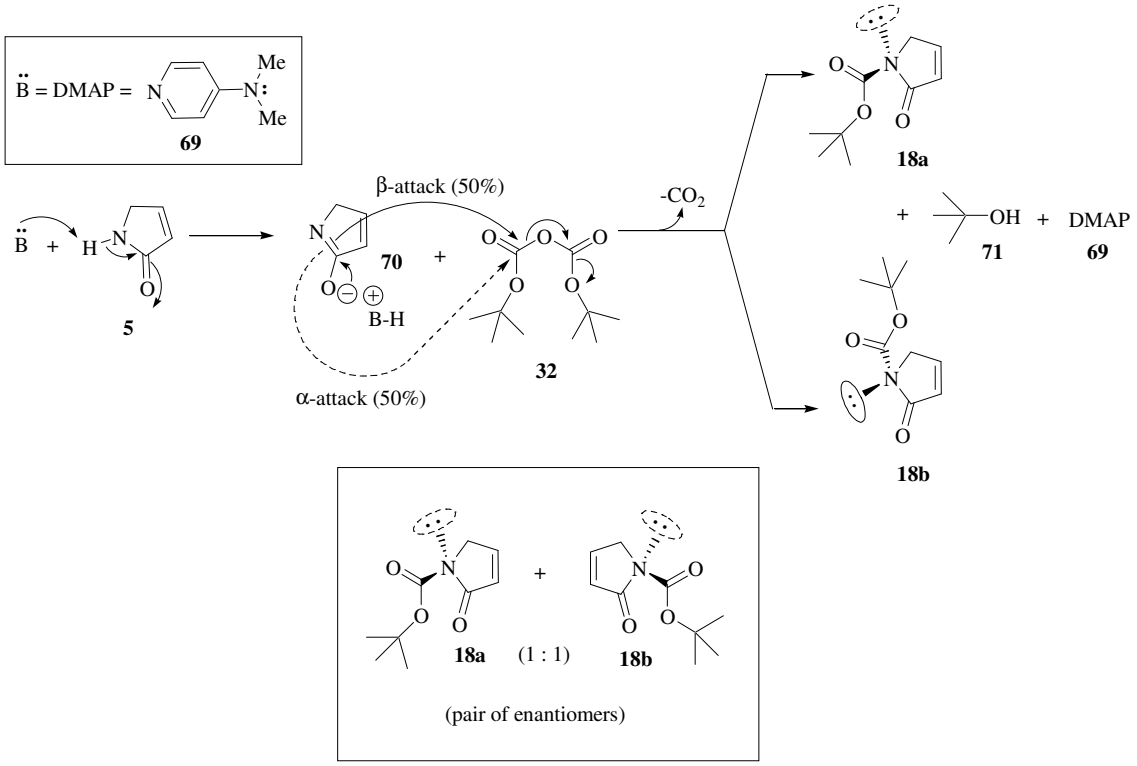


Scheme S10. Speculative mechanism for the synthesis of compound **9**.

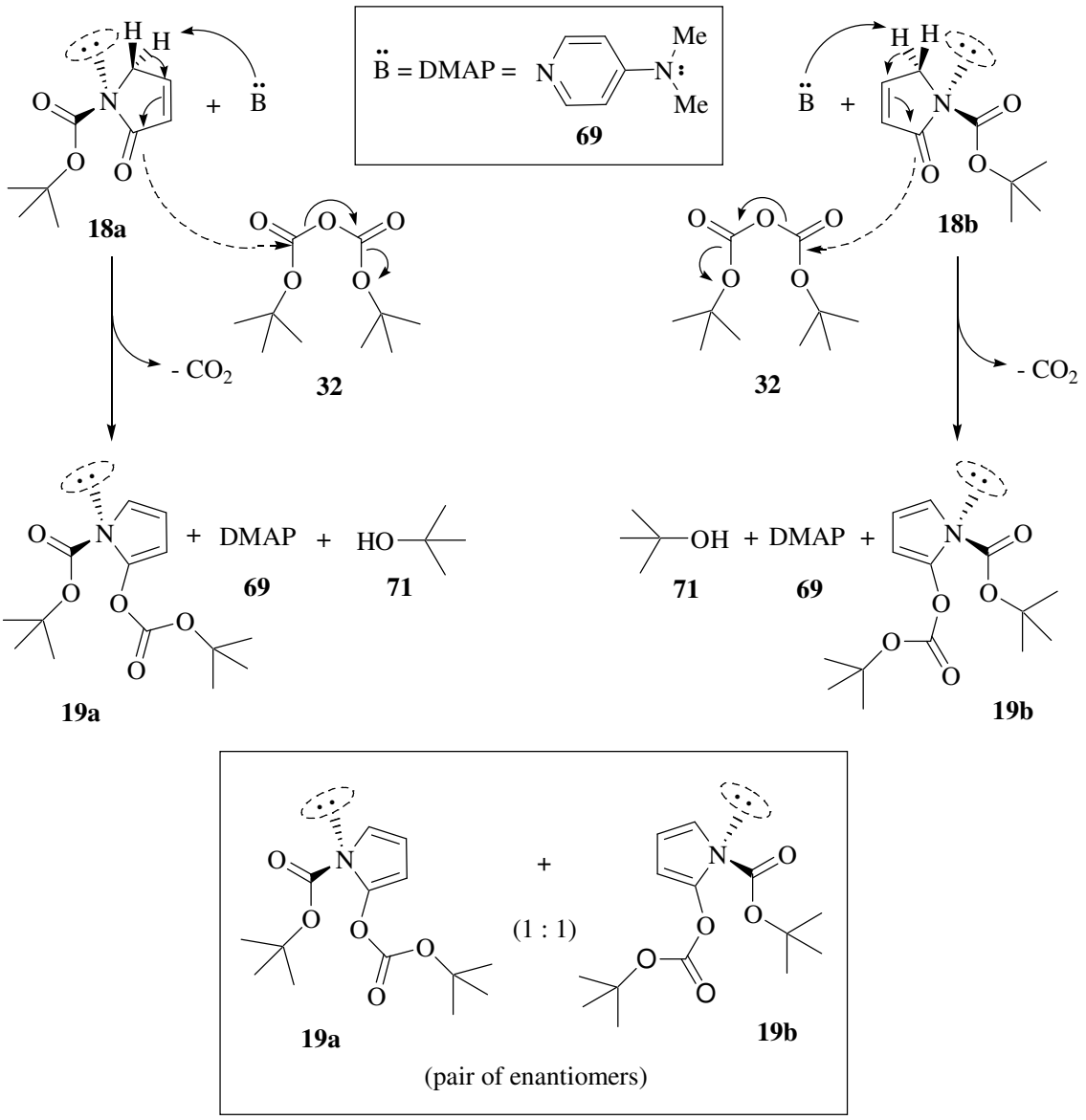
We are considering, in Scheme S10, the acid HCl as source of H^+ usually generated *in situ* by the reagent TMSCl.



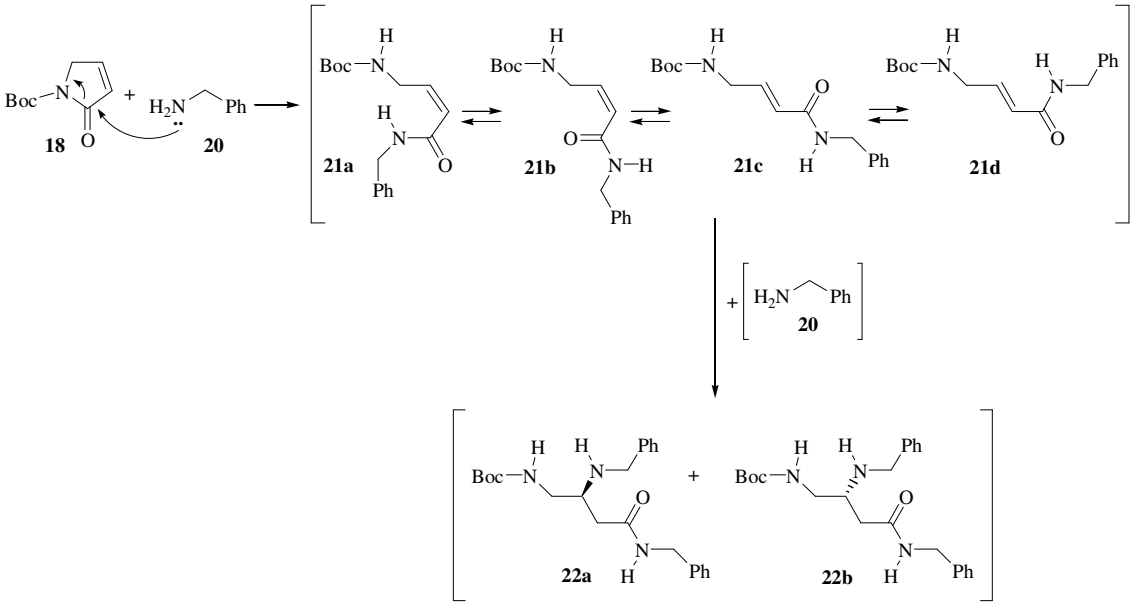
Scheme S11. Speculative mechanism for the synthesis of compound **10**.



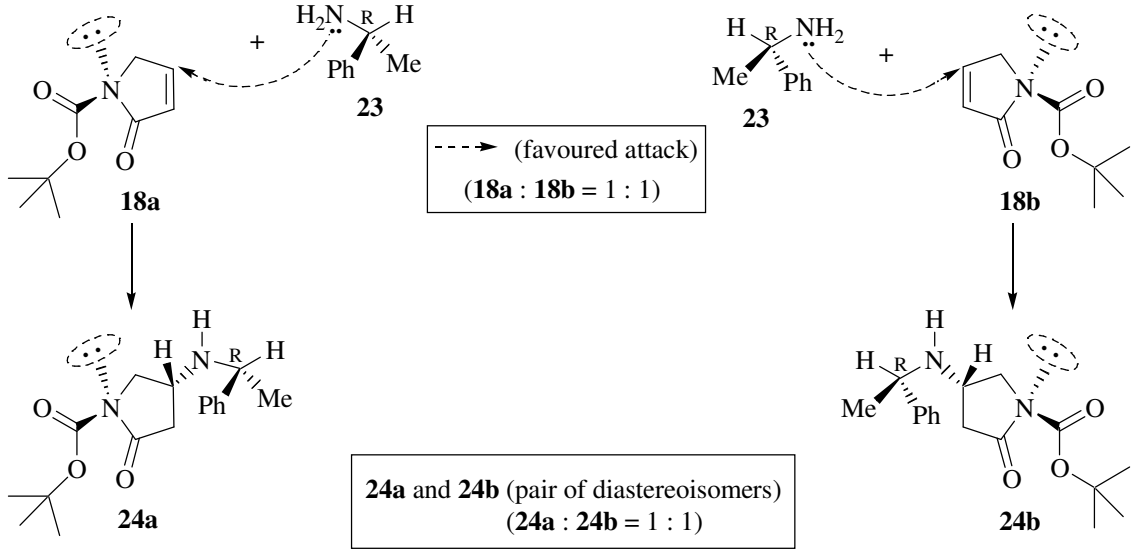
Scheme S12. Speculative mechanism for the synthesis of the isomers **18**.



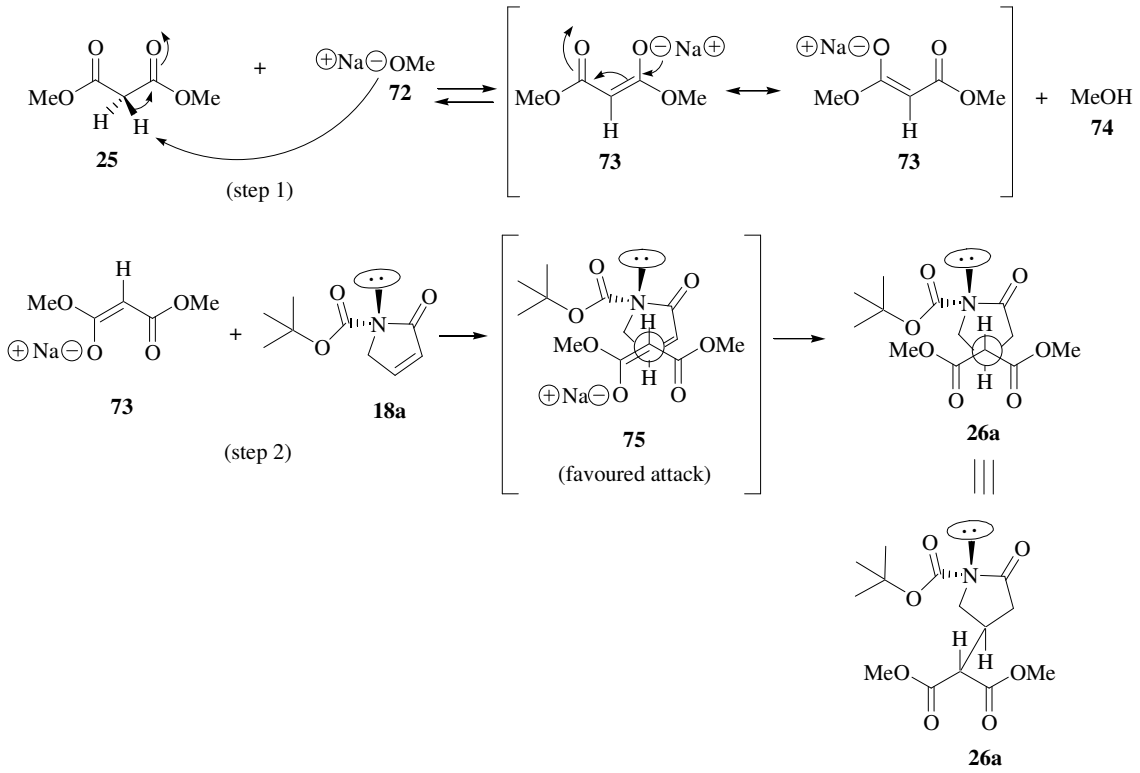
Scheme S13. Speculative mechanism for the synthesis of the isomers **19**.



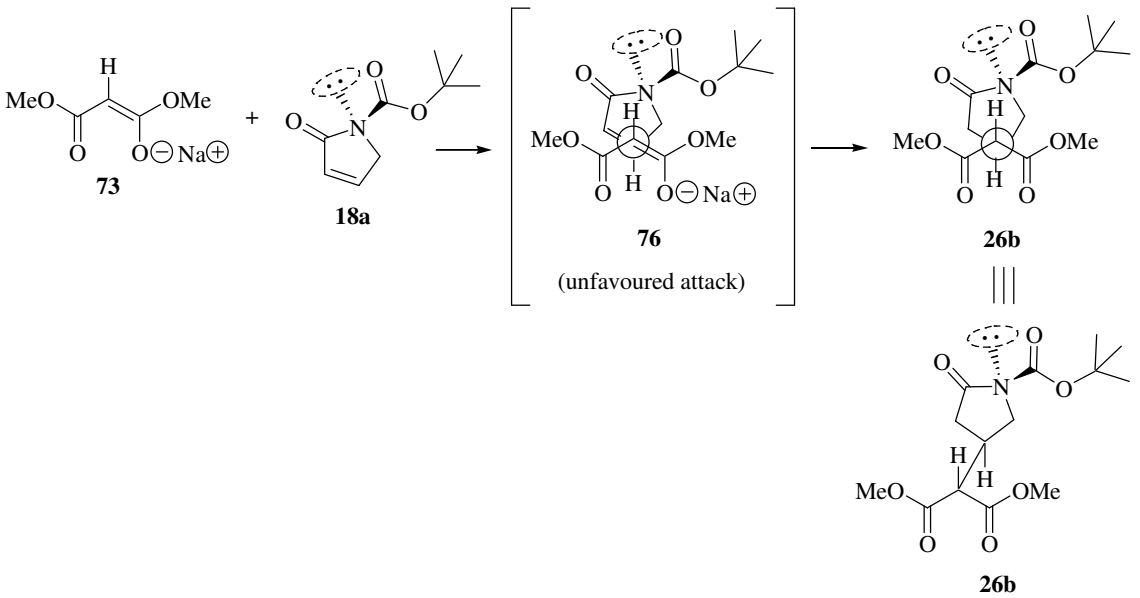
Scheme S14. Speculative mechanism for the synthesis of isomers of the butenamide **21** and butanamide **22**.



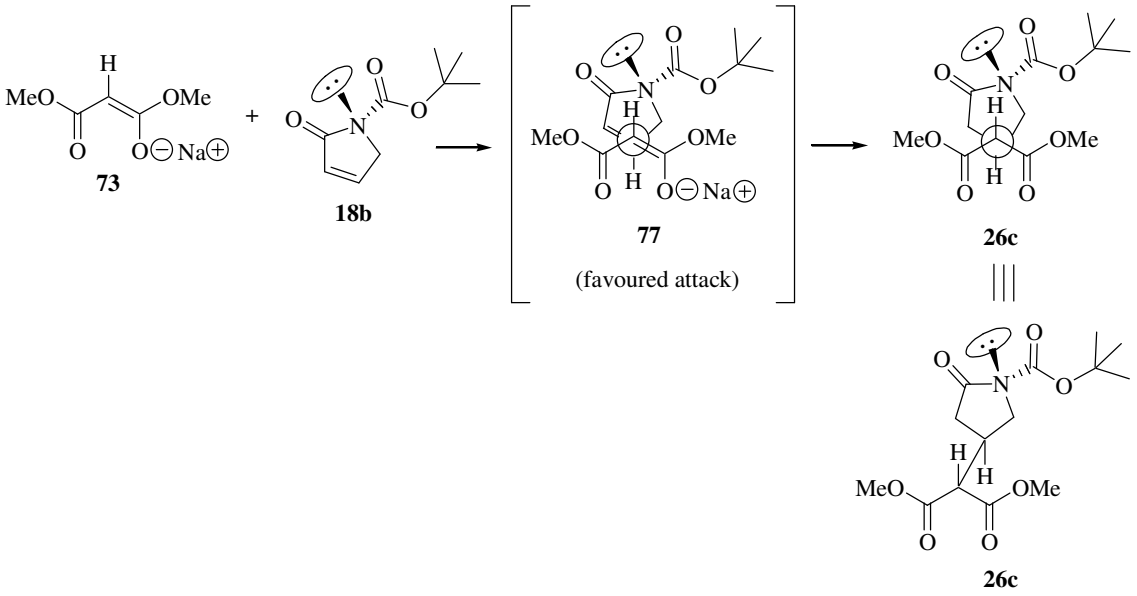
Scheme S15. Speculative mechanism for the synthesis of the isomers **24**.



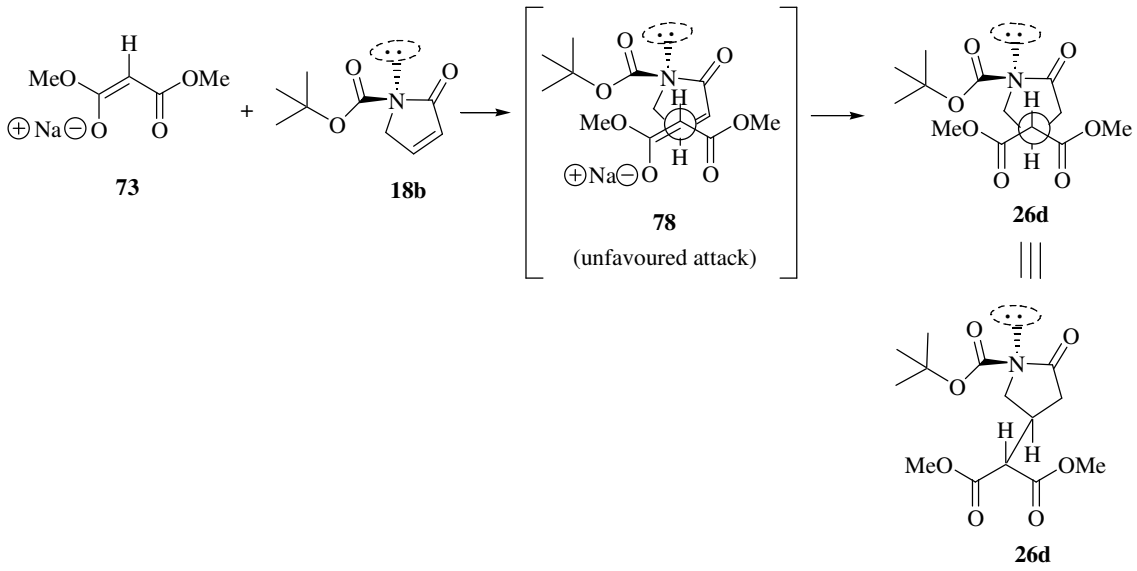
Scheme S16. Speculative mechanism for the synthesis of the *anti*-adduct **26a**.



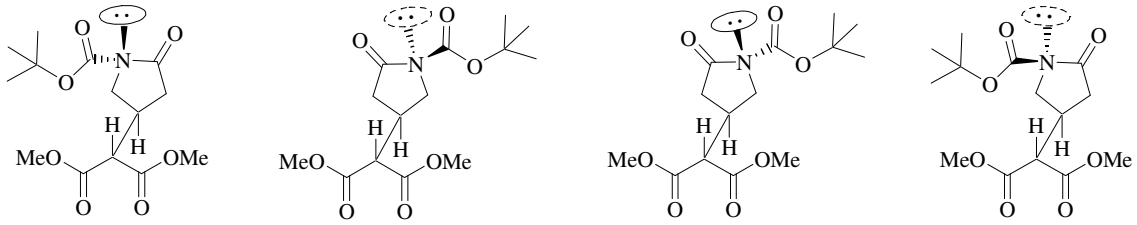
Scheme S17. Speculative mechanism for the synthesis of the *anti*-adduct **26b**.



Scheme S18. Speculative mechanism for the synthesis of the *anti*-adduct **26c**.



Scheme S19. Speculative mechanism for the synthesis of the *anti*-adduct **26d**.

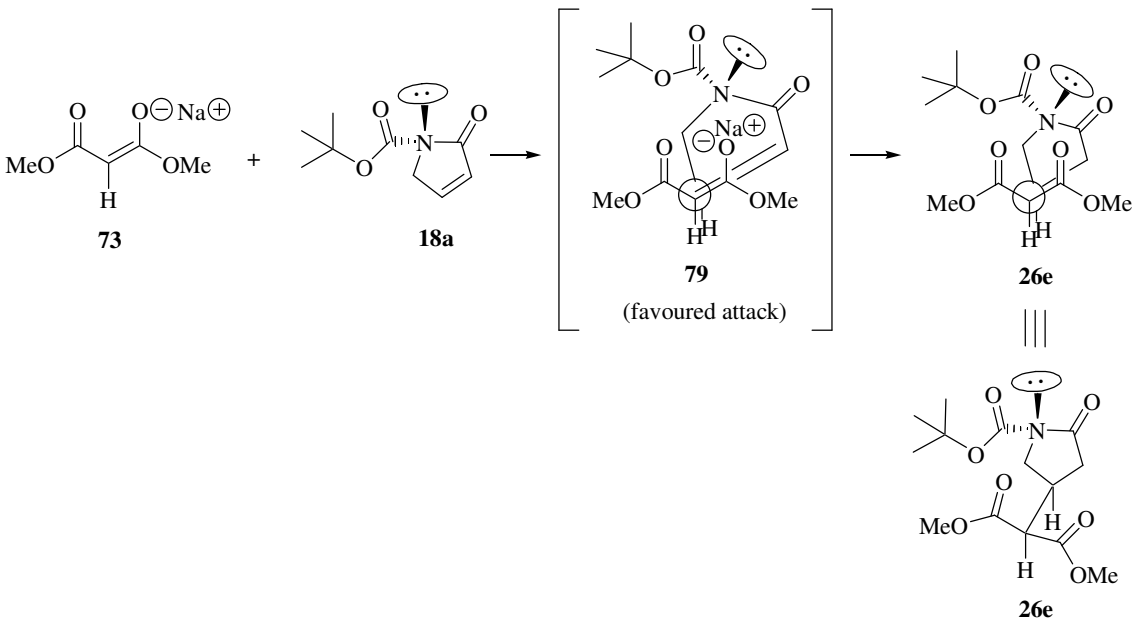


26a (major) **26b** (minor) **26c** (major) **26d** (minor)

26a and **26b** (pair of diastereoisomers)
26c and **26d** (pair of diastereoisomers)
26a and **26c** (pair of enantiomers)
26b and **26d** (pair of enantiomers)

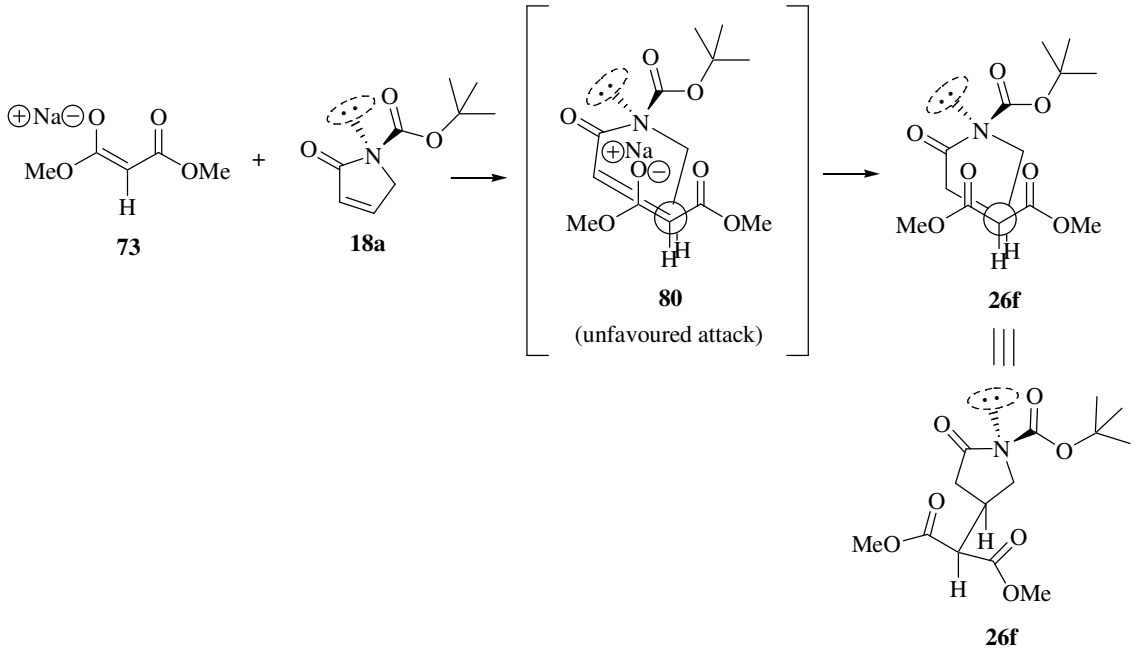
Figure S1. Probable isomers of the *anti*-adducts of malonate (**26a**-**d**).

Signals were detected at the ^{1}H NMR spectrum of **26**, and attributed to 2 *anti*-adducts in the proportion (2:1) measured by integrals relative to antiperiplanar methinic hydrogens of the groups malonyl [δ 4.12 (d, *J* 8.0 Hz, 1H, minor isomer) and δ 4.07 (d, *J* 8.0 Hz, 1H, major isomer)]. The axial-axial interactions between those hydrogens and the methinic hydrogens at C-4 position of the lactamic rings were determined by the coupling constants (*J* 8.0 Hz).

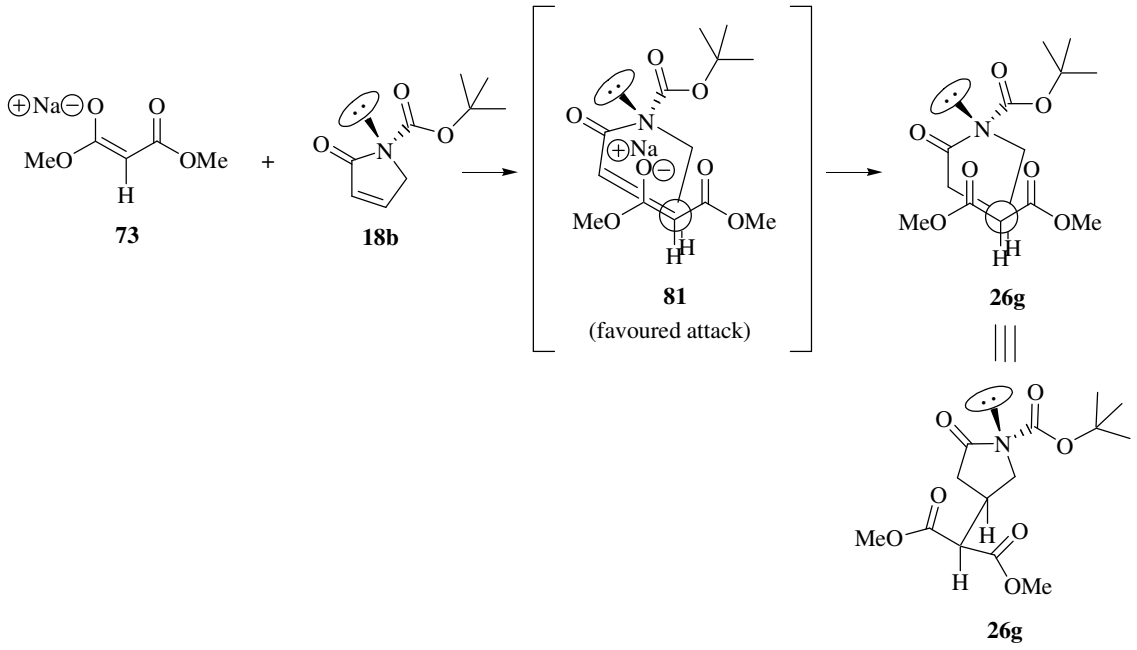


73 **18a** **79** (favoured attack) **26e** **26e**

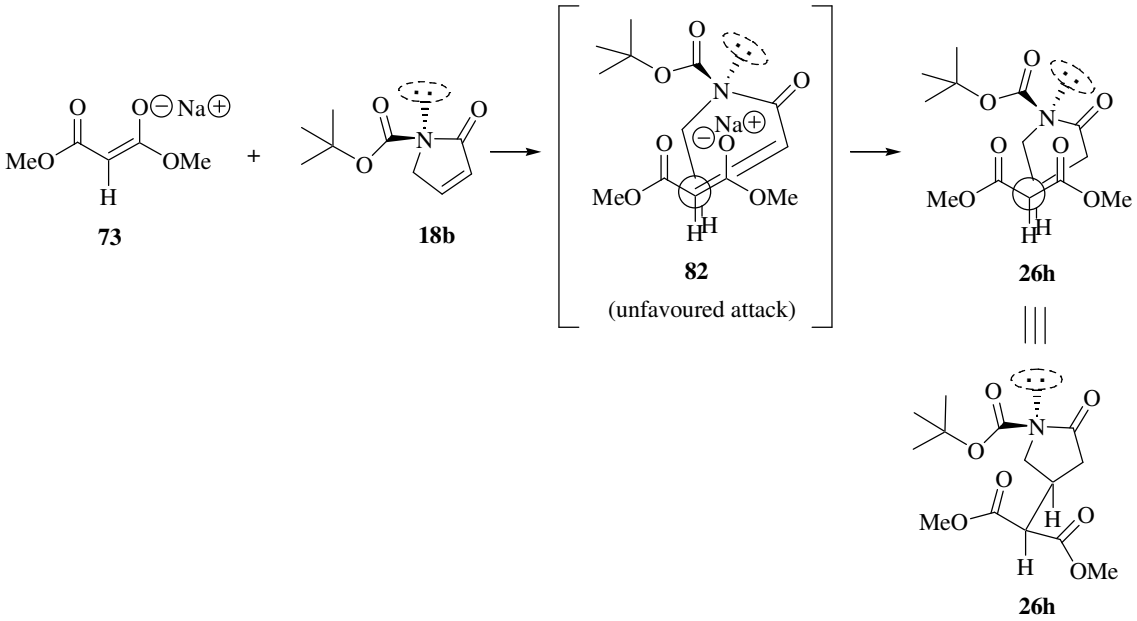
Scheme S20. Speculative mechanism for the synthesis of the *syn*-adduct **26e**.



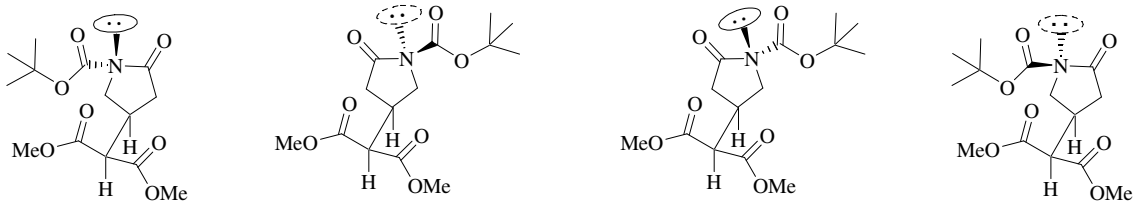
Scheme S21. Speculative mechanism for the synthesis of the *syn*-adduct **26f**.



Scheme S22. Speculative mechanism for the synthesis of the *syn*-adduct **26g**.



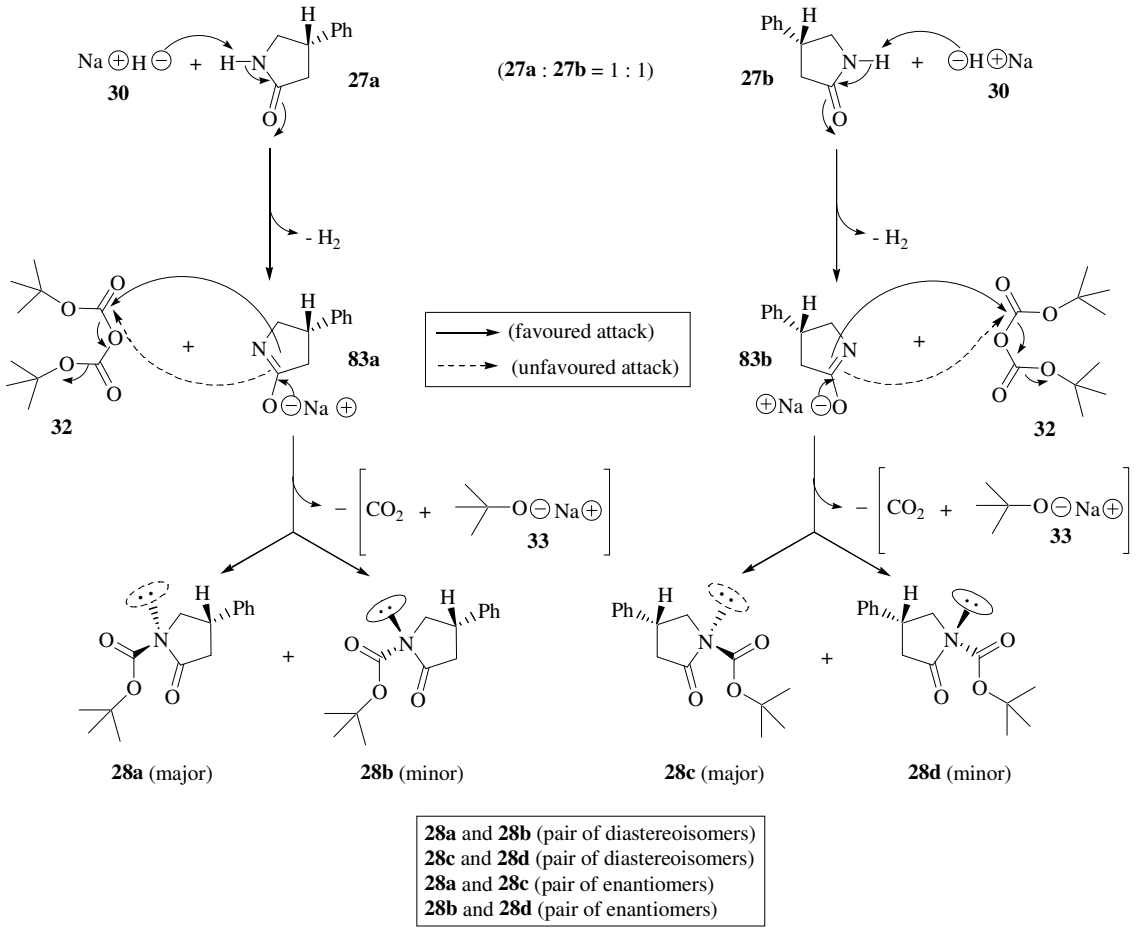
Scheme S23. Speculative mechanism for the synthesis of the *syn*-adduct **26h**.



26e and **26f** (pair of diastereoisomers)
26g and **26h** (pair of diastereoisomers)
26e and **26g** (pair of enantiomers)
26f and **26h** (pair of enantiomers)

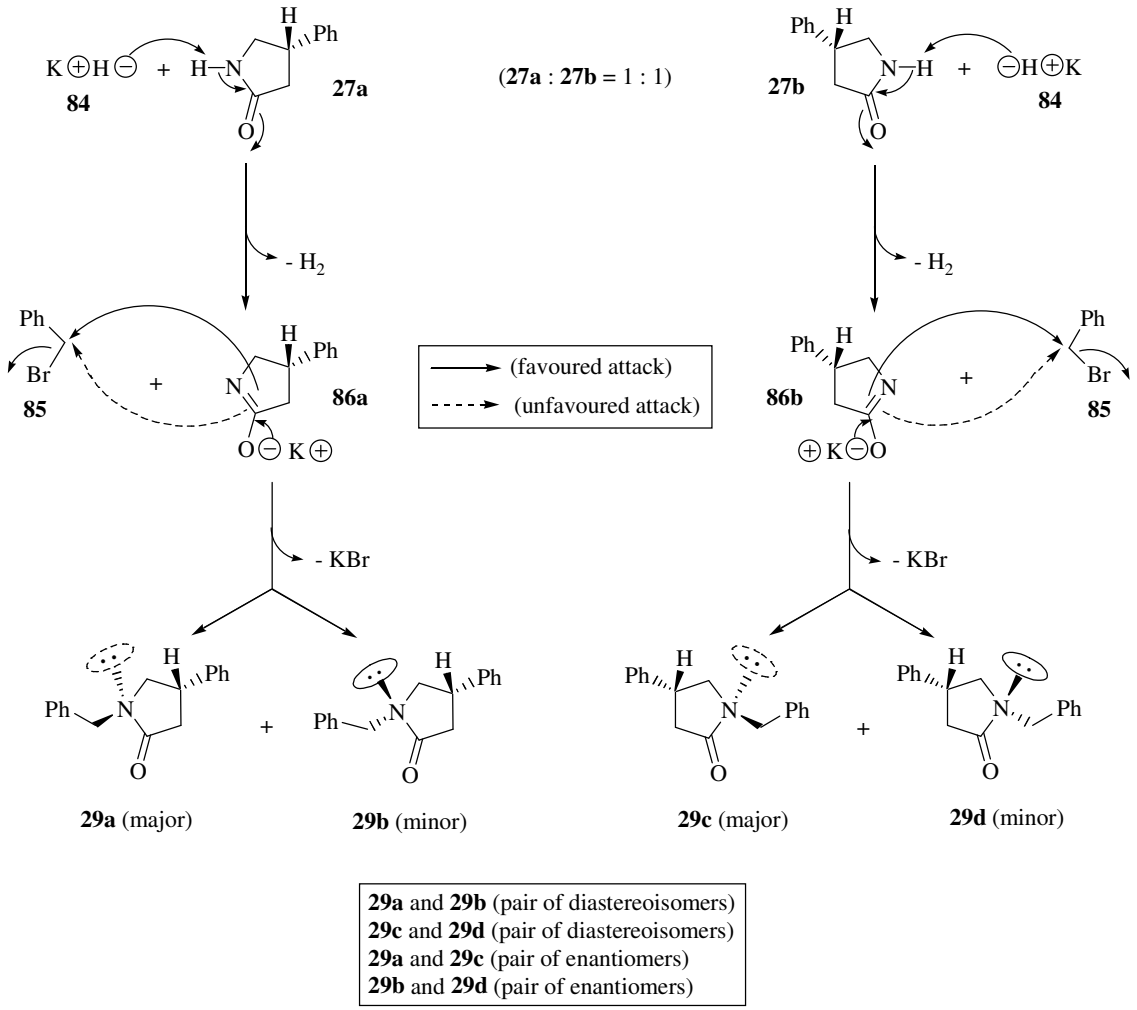
Figure S2. Probable isomers of the *syn*-adducts of malonate (**26e**-**h**).

Signals at δ 3.76 (d, *J* 3.9 Hz, 1H) and δ 3.68 (d, *J* 4.4 Hz, 1H) in the proportion (1:1) were detected at the ^{1}H NMR spectrum of **26**, and attributed to methinic hydrogens of the groups malonyl of *syn*-adducts of malonate. The equatorial-equatorial interactions between those hydrogens and the methinic hydrogens at C-4 positions of the lactamic rings were determined by coupling constants (*J* 3.9 Hz and 4.4 Hz).



Scheme S24. Speculative mechanism for the synthesis of the isomers **28**.

A minor signal at δ 1.41 was detected at the ^{1}H NMR spectrum of **28**, and attributed to the hydrogens of the methyl groups of *tert*-butoxycarbonyl. The proportion between the major (δ 1.53) and minor (δ 1.41) isomer is (12:1).



Scheme S25. Speculative mechanism for the synthesis of the isomers **29**.