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Silylated pyrrolidones via diastereoselective Pd-catalysed intramolecular allylic alkylations

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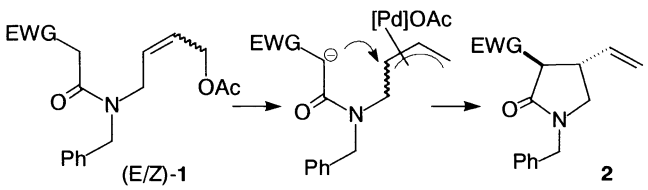
Abstract—A new palladium-catalysed allylic alkylation affording silylated 3-vinyl-pyrrolidones has been developed. The method relies upon the interaction between a stabilised acetamide enolate anion and a silicon-containing nitrogen-tethered η^3-allyl-palladium moiety. Two variants have been studied, involving location of the silicon atom on either olefinic carbon atom of the cyclisation precursor. In both cases 5-*exo*-trig ring closure was the only cyclisation process observed. These results contrast with related β-ketoester cyclisations, were competitive 7-*endo*-trig is observed. © 2001 Elsevier Science Ltd. All rights reserved.

We (G.P and G.G.) recently reported a new palladium-catalysed intramolecular allylic alkylation process[1] based on the interaction between a stabilized acetamide enolate anion and a juxtaposed nitrogen-tethered η^3-allyl-palladium appendage. This totally diastereoselective reaction constantly favoured a 5-*exo*-trig mode of cyclisation, thereby producing 3,4-disubstituted pyrrolidones (Scheme 1).

On the other hand, it is known that a trialkylsilyl group can sensibly modify the reactivity of η^3-allyl-palladium complexes. Thus, for example, Hirao and co-workers[2] were the first to report that Me_3Si-substituted η^3-allyl-palladium complexes direct the addition of nucleophiles exclusively to the distal position (relative to silicon atom), thereby leading to the corresponding vinylsilanes. Such a regioselectivity may be accounted for in terms of (a) steric factors, (b) charge distribution of the allyl complex and (c) stability of the newly formed olefin–Pd(0) complex.[3]



Scheme 1. *Reagents and conditions*: $Pd_2(dba)_3$, (0.05 equiv.), PPh_3, (0.5 equiv.), BSA (1.2 equiv.), AcOK (0.1 equiv.), THF reflux, 12 h. EWG: CO_2Me, COMe, CN, SO_2Ph, $PO(OEt)_2$.

In this context, we (M.M. and S.T.) have developed a palladium-catalysed cyclisation reaction, wherein 2-triethylsilyl-1,4-diacetoxy-but-2-ene is converted into a silyl-substituted cyclopentene.[4] In this global annulation process the role of silicon is crucial and twofold. In fact, in the former C–C bond formation the bulky trialkylsilyl donor group regiodirects the ionisation of the initial bis-allylic system, whereas in the latter one it favours the *syn* configuration of the η^3-allylpalladium complex, so as to allow an unusual 5-*endo*-trig process to take place (Scheme 2).

Given the above background we decided in a joint project to study the effect of silicon-substitution on the amide-based cyclisation. In particular, we were intrigued to verify if such modifications could still guarantee cyclisations, and, in the positive case, to determine the 5-*exo*-trig versus 7-*endo*-trig preference. In fact, such a competition in the cyclisation mode has been previously observed by Tsuji and co-workers in pioneering studies on intramolecular palladium-catalysed cyclisations (Scheme 3).[5]

Keywords: palladium and compounds; allylation; silicon and compounds.

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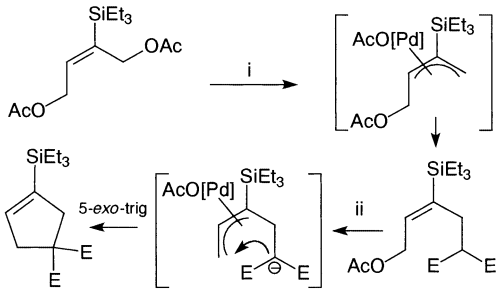
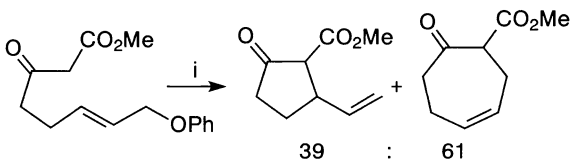


Scheme 2. *Reagents and conditions*: (i) $NaCHE_2$ (E = CO_2Me), $Pd(PPh_3)_4$ (5%), THF (85%); (ii) NaH, 5% $Pd(PPh_3)_4$, THF, 60°C, 74%.



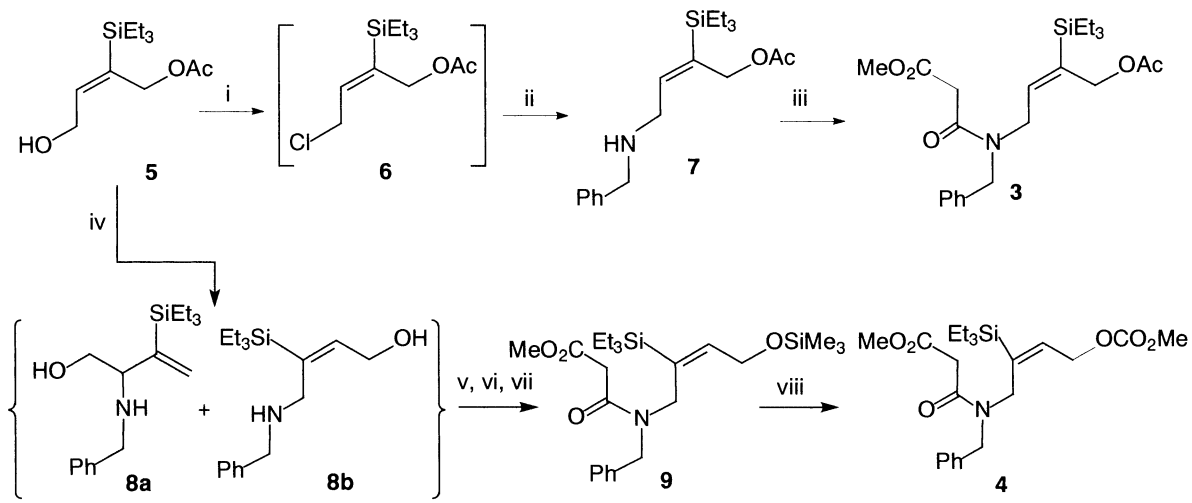
Scheme 3. *Reagents and conditions*: $Pd(OAc)_2$ (5–10%), PPh_3, THF reflux.

Accordingly, the synthesis of the two silylated cyclisation precursors **3** and **4** has been undertaken (Scheme 4). The first cyclisation precursor **3** was obtained in three steps from the silylated allylic alcohol **5**.[4a] Chlorination of the alcohol function gave the corresponding chloride **6**, which was immediately treated with benzylamine to give the secondary allylic amine **7**. Malonylation under standard conditions gave uneventfully the desired precursor **3**.

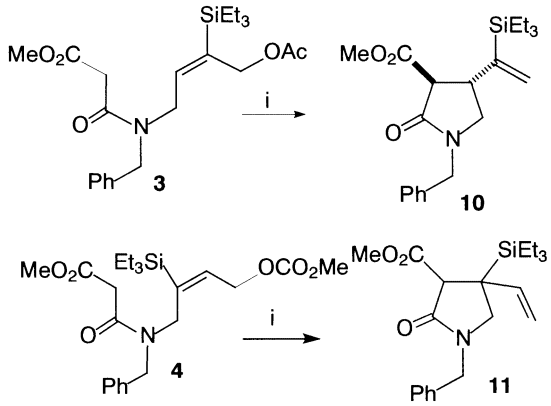
The second cyclisation precursor **4** was obtained from the same key vinylsilane **5** as used in the previous synthetic sequence. Palladium-catalysed allylic amination of **5** in the presence of benzylamine afforded the regioisomeric secondary amines **8a** and **8b** in a 24:76 ratio, the major isomer being a stereohomogeneous aminoalcohol derived from amine addition to the less substituted π-allyl terminus. At this stage the synthesis needed *N*-malonylation of the major isomer **8b** followed by *O*-derivatisation. Surprisingly, *N*-malonylation of this aminoalcohol took place with competitive *O*-malonylation. Ironically enough, treatment of the same aminoalcohol with acetic anhydride gave exclusively nitrogen acetylation! The problem was solved by temporary protection of the hydroxyl function as TMS derivative before the *N*-malonylation step. The desired precursor **4** was eventually obtained in nearly quantitative yield by treating allylic alcohol **9** with methyl chloroformate (Scheme 4).

After some preliminary and deceiving cyclisation experiments we found that treatment of the sodium enolate of **3** with 5% $Pd(OAc)_2$ and 10% diphenylphosphinoethane (dppe), in DMF at 100°C for 30 min, gave pyrrolidone **10** cleanly in a completely regio- and stereoselective way (Scheme 5). More interestingly, submission of the silylated derivative **4** to the same reaction conditions as before, gave pyrrolidone **11** as a single isomer.

The above experiments reveal the intrinsic and total preference of these substrates for a 5-*exo*-trig process over the alternative 7-*endo*-trig one, even when C–C bond formation involves reaction at the η^3-allyl terminus carrying the bulky trialkylsilyl group. Not unexpectedly, on passing from the former to the latter cyclisation an important decrease in yield is observed (90 versus 52%). Determination of the relative configuration of the cyclised products turned out to be difficult. However, thermodynamic control via NaOAc promoted equilibration has been constantly observed in our laboratory in a number of analogous reactions. Therefore, *trans* stereochemistry has been assigned to pyrrolidone **10**. Similarly, compound **11** is expected to be the most stable diastereoisomer.[6] Although for the time being the lack of knowledge of several parameters does not allow us to be more specific, some fundamen-

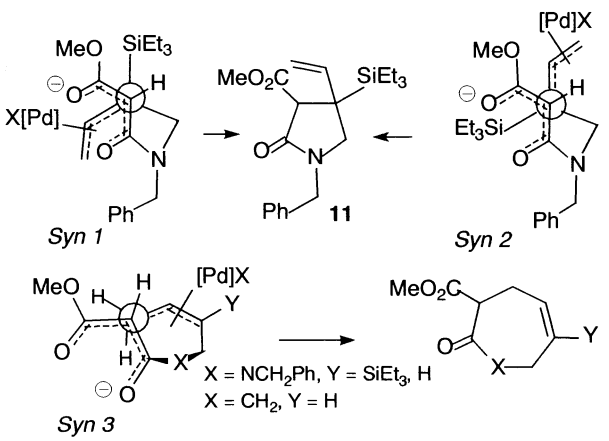


Scheme 4. *Reagents and conditions*: (i) PPh_3, CCl_4; (ii) $PhCH_2NH_2$, MeCN (63% from **5**); (iii) MeO_2CCH_2COCl, NEt_3, CH_2Cl_2 (81%); (iv) $PhCH_2NH_2$, NEt_3, $Pd(OAc)_2$ (5%), dppe (10%), THF, rt (68%); (v) Me_3SiCl, NEt_3, THF, rt; (vi) MeO_2CCH_2COCl, NEt_3, CH_2Cl_2; (vii) HCl 10% until pH 2–3, THF, rt (82% from **8b**); (viii) MeO_2CCl, pyridine, CH_2Cl_2, rt (98%).



Scheme 5. *Reagents and conditions*: (i) $Pd(OAc)_2$ (5%), dppe (10%), NaH, DMF, 100°C (90% **3**→**10**, 52% **4**→**11**).

tal stereochemical speculations can already be put forward. In accord with what has been previously observed, we assume that the relevant reactive conformations associated with the latter cyclisation are *syn*-1 and/or *syn*-2 (Scheme 6), wherein the bulky silicon atom occupies the *syn* position[7] and the rest of the chain is forced to occupy the *anti* position. Although the two approaches lead to different diastereoisomers, deprotonation after C–C bond formation is expected to drive the equilibrium toward the most stable diastereoisomer. In addition, the constant and exclusive formation of pyrrolidone structures from these amides suggests that, contrary to the related Tsuji's β-ketoesters cyclisations, the only plausible 7-*endo*-trig type approach *syn*-3 has to be highly disfavoured with respect to *syn*-1 and/or *syn*-2. Indeed, inspection of models reveals that *syn*-3 approach needs an appropriate C–C–X–C dihedral angle value. Although such a requirement may be easily met with β-ketoesters (X = CH_2), in the case of amidoesters (X = NCH_2Ph) the flat nature of the amide bond is expected to force C–C–X–C dihedral angle values close to 0 or 360°, thereby disfavouring the *syn*-3 approach and its related 7-*endo*-trig cyclisation.[8]



Scheme 6. Relevant reactive conformations in the palladium-catalysed intramolecular allylic alkylation of silylated amidoester **4**, and comparison with β-ketoester cyclisation.

In summary, this new investigation showed that the formal introduction of a trialkylsilyl group into either position of the double bond in the precursor still permits the cyclisation to take place. As in the previous studies only 5-*exo*-trig cyclisations are observed, thereby producing 3-vinyl-pyrrolidones silylated at strategic positions. In both the cases studied the reactions were completely diastereoselective. Further modifications of the obtained pyrrolidones via the rich chemistry of allyl- and vinyl-silanes[9] is planned in future studies.

Acknowledgements

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