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Revision of the stereochemistry of the reductive Heck cyclisation of 1-(2-iodobenzoyl)-4-substituted-1.4-dihydro-pyridine-3-carbaldehyde aminals

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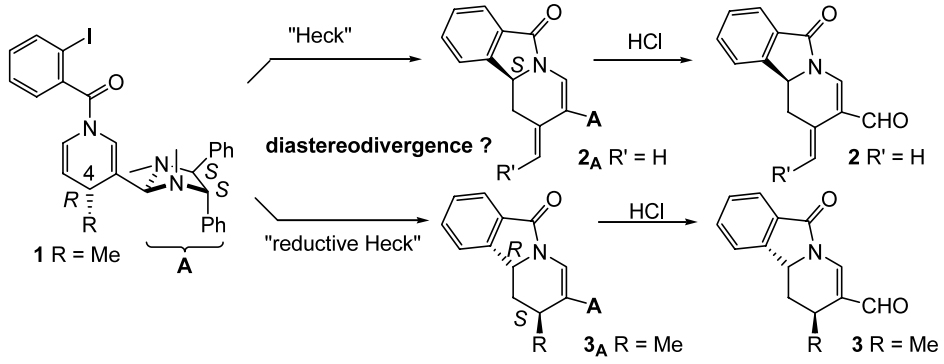
Abstract—The stereochemistry of reductive and non reductive Heck cyclisations of 4-substituted-1.4-dihydropyridines is reexamined. The both reactions occur mainly *via* an *anti* (from the C_4 substituent) 5-*exo* process without any epimerisation of the C_4-H.

We recently reported unexpected results obtained by Heck cyclisations of a functionalised 1,4-dihydropyridine **1**.[1] It was claimed in this paper that a non reductive (Heck) cyclisation afforded, after removal of the aminal, a compound **2** resulting from an *anti* carbopalladation and that a reductive Heck cyclisation yielded to a compound **3** resulting from a *syn* carbopalladation with an epimerisation of the C_4-H (Scheme 1). The structures of these two cyclised products **2** and **3** were established on the basis of X ray analysis of the aminals $\mathbf{2_A}$ and $\mathbf{3_A}$.[2] This unexpected interesting result impelled us to study the possible influence of the nature of the substituent R on the stereochemistry of these reactions.

Accordingly, two dihydropyridines **4** (R = Et) and **5** (R = Ph) were prepared (Scheme 2). The addition of EtCu to the pyridine aminal **6** in the presence of ortho-iodobenzoyl chloride gave a complex mixture resulting from a non regio- and diastereoselective addition. Several attempts to increase these selectivities by changing the nature of the copper salt were ineffective affording the same surprising result. Indeed, we have never observed, in similar reaction, such poor selectivities using primary alkyl copper reagents.[3] As a last resort, the dihydropyridine **4** was prepared from **7**, easily prepared from **6**, by a selective addition of EtCu in the presence of acetyl chloride and then transacylation according Scheme 2.[4] The dihydropyridine **5**



Scheme 1.

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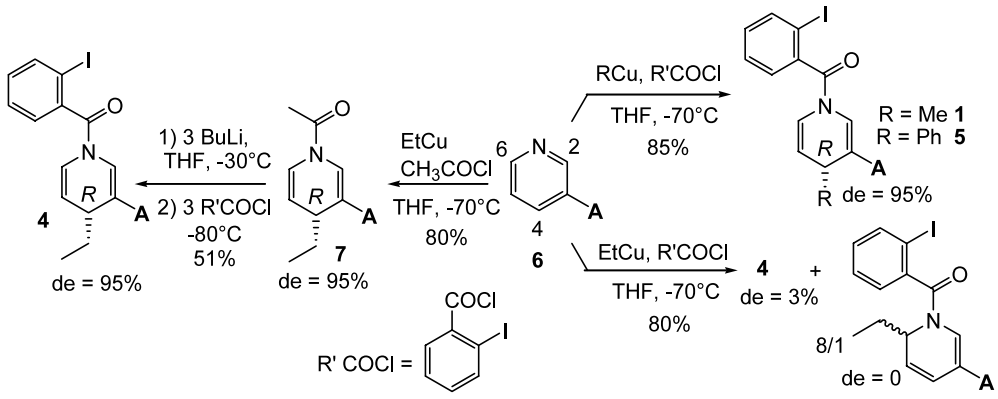


Scheme 2.

was obtained by a selective addition of PhCu to **6** in the presence of ortho-iodobenzoyl chloride.

A Heck cyclisation (Scheme 3) was attempted on dihydropyridines **4** and **5**. A clean reaction was observed with **4** affording a mixture of *Z* and *E* cyclised products **8** (de>90%, ^{1}H NMR, Scheme 3). Under the same conditions, **5** gave a complex mixture. In reductive conditions two cyclised adducts **9** were produced from **4**, as a mixture (9/1) of *trans* and *cis* diastereomers (de>90% each, ^{1}H NMR) and from **5** only one compound **10** was obtained (de>90%, ^{1}H NMR). The results observed with **4** were apparently similar to those reported in our previous report starting from **1**, but this was not the case with the phenyl-dihydropyridine **5**. Therefore, the structure of **10** was determined by X ray analysis.[5] As shown in Figure 1, the absolute stereochemistry of this compound was found to be C_4-(*R*) and C_6-(*S*) starting from an aminal of *S*,*S* configuration. Therefore, **10** was the result of an *anti* carbopalladation without epimerisation of the C_4-H. This disturbing result was attributed, in first analysis, to the presence of a phenyl substituent. Therefore, we attempted to crystallise the *trans* **9** for X-ray analysis but without success. Finally, we decided to reproduce the reductive Heck cyclisation with **1** as described in our previous paper (Scheme 3). Two cyclised products **11** were obtained as a *trans* and *cis* mixture in a 7/3 ratio (de>90% for each, ^{1}H NMR). The major *trans* diastereomer was purified by chromatography and crystallised. The NMR spectra (^{1}H and ^{13}C) of this compound were found to be identical to those obtained in our previous study but an X-ray analysis (Fig. 2)[6] showed that it was not the result of a *syn* carbopalladation with epimerisation of the C_4-H, but similarly to **10**, of an *anti* carbopalladation without epimerisation of the C_4-H to give a C_4-(*R*) and C_6-(*S*) adduct. An acidic hydrolysis gave the corresponding aldehyde **12** which optical rotation was found to be identical to the one reported previously.[1]

This aldehyde **12** was then treated by the *R*,*R* diamine **13** to give the aminal **14** (Scheme 4). The ^{1}H NMR spectra of **11** and **14** were found to be different to each other.

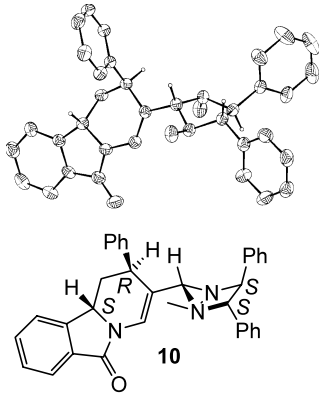
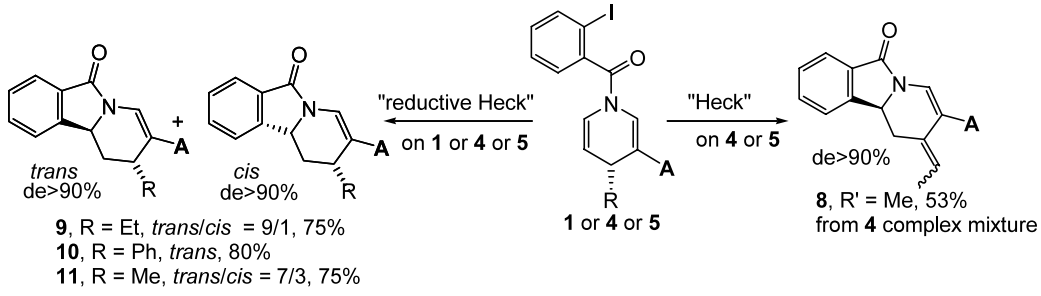


Figure 1.



Scheme 3. 'Heck': $Pd(OAc)_2$ 10%, AcOK, DMF, 90°C, 4 h; 'reductive Heck': $Pd(OAc)_2(PPh_3)_2$ 10%, HCOOH, piperidine, CH_3CN, 80°C, 4 h.

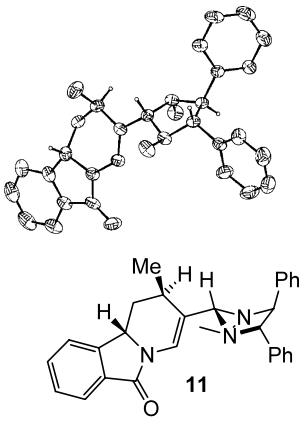


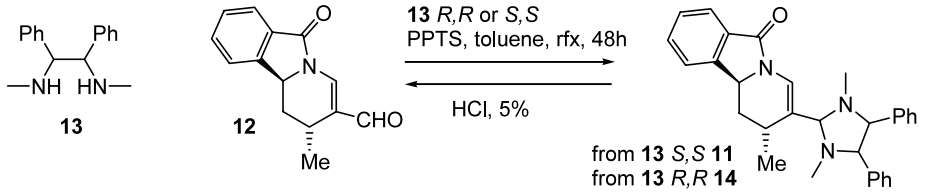
Figure 2.

The only conclusion it was possible to draw back from all these results is that our previous observation of a stereodivergence between reductive and non reductive Heck cyclisations[1] was not confirmed. In fact, the two reactions occur mainly *via* an *anti* carbopalladation (from the C_4 substituent).

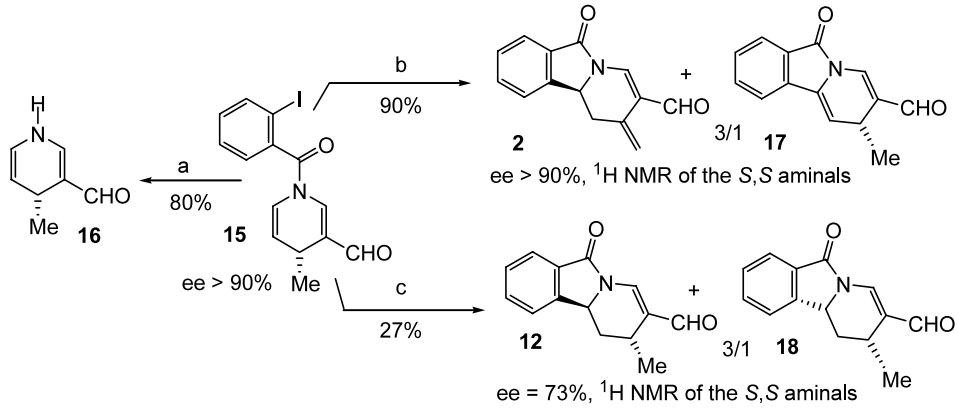
Additionally, we have checked that the presence of a chiral aminal did not change the stereochemical outcome of the reaction by performing reductive and non reductive Heck cyclisations on the aldehyde **15**[7] obtained by acidic hydrolysis of **1** (Scheme 5).

A change of the conditions for the non reductive Heck cyclisation of the aldehyde **15** was needed due to the fast cleavage of the amide bond by AcOK yielding to **16** (Scheme 5). In the presence of 10% of $Pd(OAc)_2(PPh_3)_2$ and 2 equiv. of iPr_2NEt in acetonitrile at 82°C, **15** yielded to a mixture of two cyclised products (3/1 ratio) in a very good yield. The major one (ee>90%) was found to be identical with **2**, the cyclised product obtained from **1** by a non reductive Heck cyclisation and hydrolysis of the aminal. A catalytic hydrogenation of the minor compound **17**[7] (ee>90%) afforded an aldehyde **18**[7] identical with the aldehyde obtained by acidic hydrolysis of *cis***11** (Scheme 6).

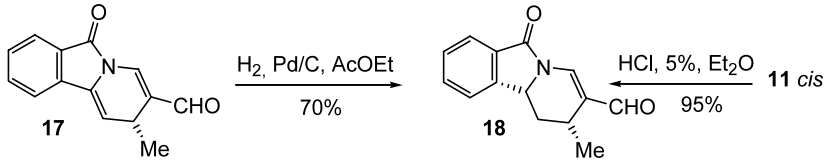
Under the reductive conditions, two aldehydes in a 3/1 ratio were obtained in poor yield (Scheme 5). The major one was identical with **12** and the minor one with **18**. Therefore, the stereochemical outcome of the reductive and non reductive cyclisations was not influenced



Scheme 4.



Scheme 5. a = $Pd(OAc)_2(PPh_3)_2$ 10% AcOK, DMF, 90°C, 4 h. b = $Pd(OAc)_2(PPh_3)_2$ 10%, 2 equiv. iPr_2NEt, CH_3CN, 82°C, 1 h. c = $Pd(OAc)_2(PPh_3)_2$ 10%, 4 equiv. piperidine, 3 equiv. HCOOH, CH_3CN, 82°C, 1 h.



Scheme 6.

by the presence of the aminal even if a loss of the enantiomeric purity was observed.

In conclusion, we have observed a strong effect of the nature of the acyl chloride used for the preparation of the 1,4-dihydropyridine **4**. We have found that the intramolecular Heck reactions, applied to such dihydropyridines, are always regioselective. We have never observed the formation of products resulting from a cyclisation onto the C_2–C_3 double bond. Furthermore, contrary to our affirmation in our first report, they occur both mainly *via* an *anti* (from the C_4 substituent) 5-*exo* process without any epimerisation of the C_4-H. This stereochemistry is independent of the presence of the aminal.

Acknowledgements

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References

1. Pays, C.; Mangeney, P. *Tetrahedron Lett*. **2001**, *42*, 589–592.
2. Probably on a wrong sample.
3. We have always obtained regio and diastereoselective additions of alkyl copper reagents on acyl pyridinium salts derived from **6**. See: Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem*. **1994**, *59*, 1877–1888; Mangeney, P.; Hamon, L.; Raussou, S.; Urbain, N.; Alexakis, A. *Tetrahedron* **1998**, *54*, 10349–10362. In one case, with an ethoxyvinyl copper reagent, we have observed that the selectivities were dependent of the nature of the acyl chloride, see Ref. 3.
4. Raussou, S.; Gosmini, R.; Mangeney, P.; Alexakis, A.; Commerçon, M. *Tetrahedron Lett*. **1994**, *35*, 5433–5436.
5. Crystallographic data have been deposited at the Cambridge Data (no. CCDC 199720).
6. Crystallographic data have been deposited at the Cambridge Data (no. CCDC 199721).
7. **15**: $[\alpha]_D^{25}=-110$ ($c=0.4$, $CHCl_3$), **17**: $[\alpha]_D^{25}=-9$ ($c=0.5$, $CHCl_3$), **18**: $[\alpha]_D^{25}=-387$ ($c=0.9$, $CHCl_3$).