The quest for the identification of the catalyst that favored the diastereoselective annulation reaction.

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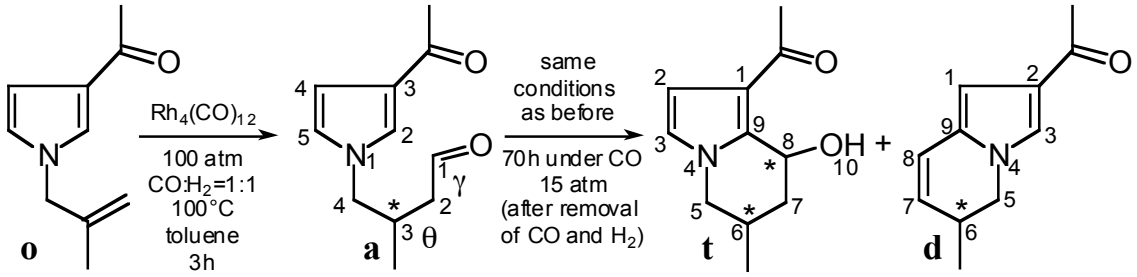
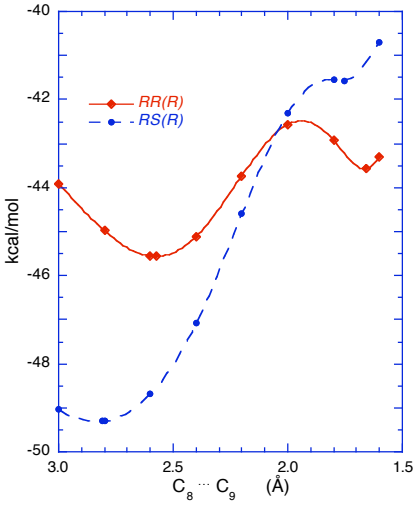
The generation of a new stereocenter with the aid of a chiral catalyst or by substrate-based asymmetric induction is an interesting topic, especially if the involved processes match criteria of atom economy. Olefin hydroformylation, incorporated into a domino-sequence, would be the ideal transformation if stereoselectivity could be controlled. The hydroformylation of the prochiral substrate (**o**) produced a new example of complete 1-3 substrate-induced diastereoselectivity: **t** (coming from intramolecular cyclization of the chiral aldehyde intermediate **a** on the 2-pyrrole position) was actually obtained as the sole diastereomer with the same absolute configuration at C6 and C8, confirmed via NMR (^{1}H, ^{13}C) and IR spectra [1].



Our investigation is aimed at understanding the origin of this amazing selectivity and at identifying the likely catalyst since high barriers (~70 kcal/mol) were computed for the uncatalyzed reaction potential energy surface (PES) at the B3LYP/6-31G* level. Using H^+ as a catalyst, the cyclization spontaneously occurs as confirmed by the experiment carried out in the presence of HCl(g) although the reaction proceeded further till dehydration also for **t** (as normally happens for the annulation on the 5-pyrrole position, which leads directly to **d**).

One of the species in the autoclave thus acts as a catalyst, but which one? In order to reduce the computational cost of PES calculations, we resorted to a very simplified model of the catalyst, Rh^+. With Rh^+ as a tentative catalyst, despite the rough approach (a bare Rh^+ does not exists), a substantial difference between the RR adduct and the RS one emerged: in the RS adduct Rh^+ takes a very favorable bifurcated arrangement between the aldehyde and ketone carbonyl groups, whereas in the RR adduct this arrangement is prevented by the different orientation of the aldehyde carbonyl group. Therefore, due to the great stability of the RS adduct, a barrier for RS much higher than that for RR is obtained.



Exploiting a more realistic model of the catalyst, such as $[Rh(CO)_3]^+$, i.e. a cationic carbonyl complex of Rh(I) [2], the potential energy profiles for the RR and RS pathways have been considered, obtaining for the latter a barrier thrice as high as that for RR (in the figure), thus explaining the reason why only the alcohol with the same chirality on both asymmetric centers (C_6 and C_8) is produced. In conclusion, a convincing explanation for the observed diastereoselectivity was put forward exploiting the knowledge gained using just a bare Rh^+.

Computational details. B3LYP hybrid functional coupled to 6-31G* basis set on all atoms except on Rh, where Hay & Wadt pseudopotentials (implicitly including some relativistic effects for core electrons) in the LANL2DZ valence basis set have been used.

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1. R. Settambolo, S. Rocchiccioli, R. Lazzaroni and G. Alagona, *Lett. Org. Chem.*, **2006**, *3*, 10.
2. With H– $Rh(CO)_3$ no RR or RS stable complex was obtained.