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Interplay of synthesis and mechanism in asymmetric homogeneous catalysis*

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Abstract: Asymmetric homogeneous catalysis forms one of the main planks of modern organic synthesis. It has developed rapidly and largely through the application of novel ligands, whose design is very much based on insight and intuition. At the same time, a better understanding of catalytic reaction mechanisms can contribute to further progress, since it can identify the intimate relationship between ligand structure and successful applications. The presentation will concentrate on the author's research with complexes of the late transition metals and include the search for superior methodologies in hydroboration, as well as ventures into the chemistry of reactive intermediates. The latter will be exemplified from work with rhodium and palladium catalysts.

APPROACHES TO TETRAHYDRONAPHTHALENE SYNTHESIS

Catalytic asymmetric hydroboration with complexes of the Rh-Quinap family is capable of providing catecholboranate adducts of vinylarenes in high enantiomer excess [1,2]. This conventionally leads via oxidation to the synthesis of secondary benzylic alcohols, although recent work has extended the range by first converting the CB adduct into a trialkylborane by reaction with diethylzinc or methylmagnesium chloride. This intermediate product is then sufficiently reactive to participate in conventional borane transformations, especially to primary and secondary amines. Both occur with essentially complete retention of the configuration of the catecholborane adduct [3].

The possibility of kinetic resolution when a racemic chiral vinylarene is employed had not previously been addressed. If successful, this could lead to interesting and active compounds in the hydronaphthalene series, for example, the antidepressant Sertraline which is marketed as a single enantiomer. The projected synthesis of this compound is shown in Scheme 1. This raises three distinct questions that need to be resolved: the synthetic route to the precursor, the protocol for hydroboration, and the conversion of the hydroboration product to the desired target molecule. The simplest route to the intended precursor on paper is a Heck reaction between dihydronaphthalene and an aryl electrophile. Such has been the intensity of effort in this field over the past four years [4], we anticipated that finding the right conditions for preparing the desired alkene would be straightforward.

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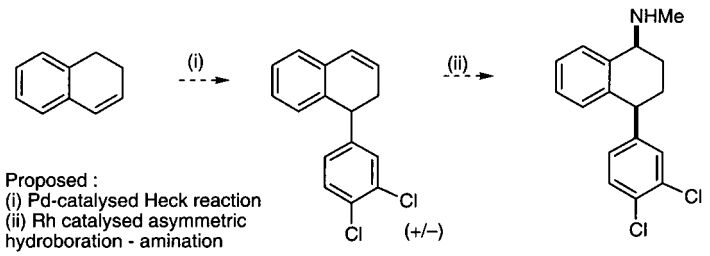
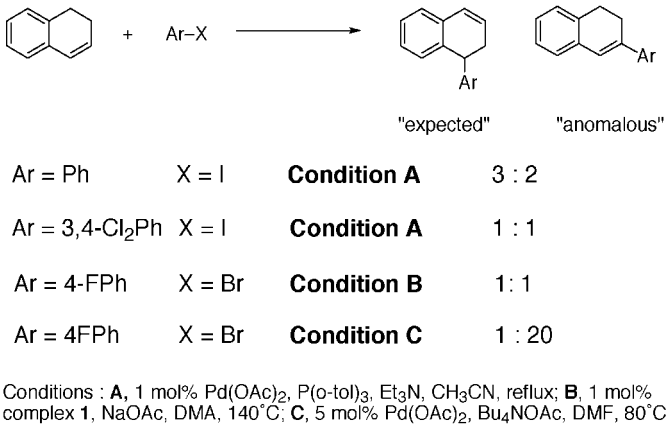


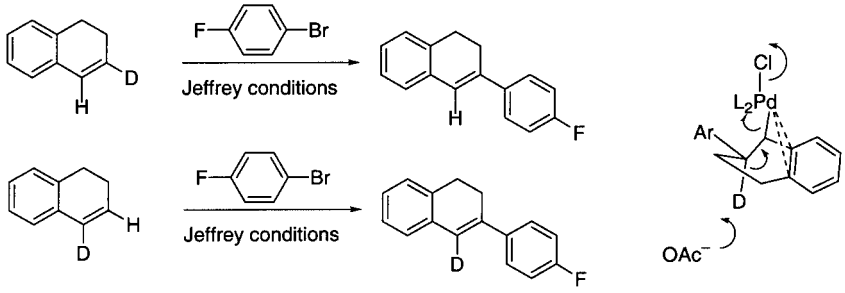
Scheme 1

It was thus a surprise to discover that the main product formed under some conditions was derived from the alternative regioisomer of arylpalladation; for different reagents and aryl precursors the proportions of the two products varied between 3:2 and 1:20, with the most pronounced bias toward the anomalous isomer being observed under the conditions introduced by Jeffrey [5]. The pathway by which a stilbene-type product is formed is not obvious, and could involve a formal *trans*-elimination [6], or alternatively a palladocarbene mechanism after that observed in Stille coupling by Busacca, Farina, and respective coworkers [7] (Scheme 2).



Scheme 2

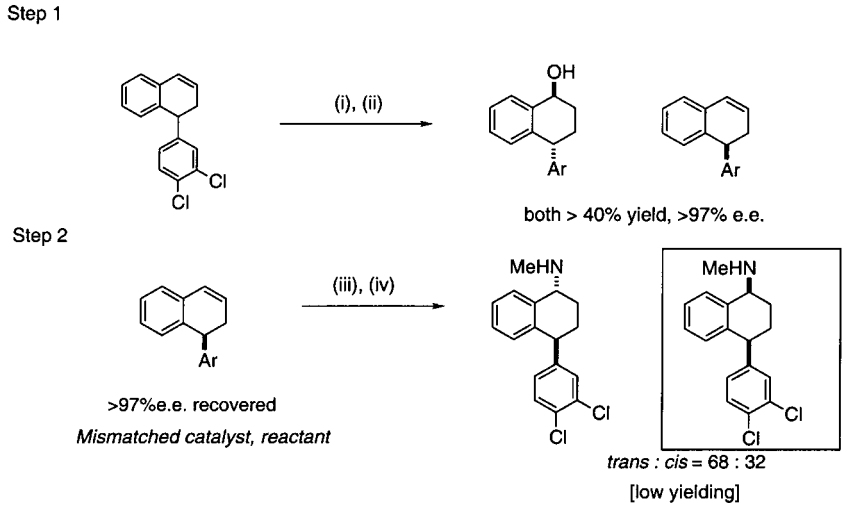
In order to distinguish between these, the 1- and 2-deuteriodihydronaphthalenes were synthesized by elimination from the corresponding alcohols, easily prepared. In separate experiments, they were subjected to Heck reaction with p-fluorobromobenzene using either “Jeffrey” or “Herrmann” conditions; the former is exemplified (Scheme 3).



Scheme 3

The results are reasonably straightforward to interpret and show that >90% of the reaction occurs through a formal *trans*-elimination of Pd–H in the pathway to the anomalous isomer. The best precedent for this stems from the observation of a *trans*-elimination mechanism competing with allylic alkylation [6,8]. The analogy requires that the arene of the reactant is not innocent in our case, and that an η^3-benzyl intermediate, well precedented in palladium chemistry [9], is probably involved.

The hydroboration proceeded smoothly under the defined conditions (Scheme 4) with very good enantiomer discrimination, leading to a successful kinetic resolution and recovery of enantiomerically pure alkene. The product from hydroboration/oxidation was predominantly *trans*-alcohol (the substituents in Sertraline are *cis*). A formal synthesis has been completed by hydroboration/amination, but a more practical route will entail a noncatalytic final step.

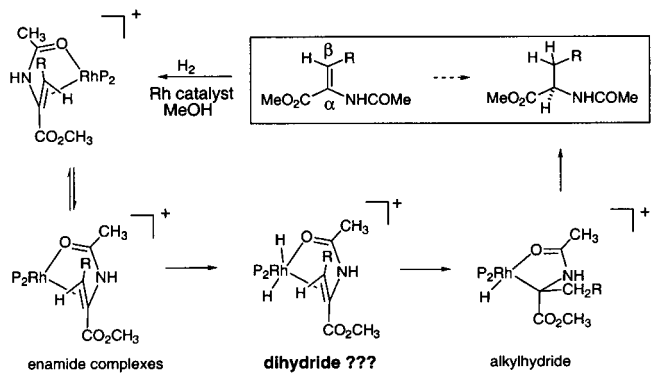


Conditions : (i) Catecholborane (0.6 eq.), *S*-QuinapRh catalyst, C_7H_8, 2 h., (ii) H_2O_2, NaOH, H_2O; (iii) Catecholborane (1.2 eq.), *S*-QuinapRh catalyst, C_7H_8, 48 h.; (iv) Et_2Zn, C_7H_8, then MeNHCl (in situ), Et_2O.

Scheme 4

INTERMEDIATES IN ASYMMETRIC HYDROGENATION

The main published efforts to discover the mechanism of rhodium asymmetric homogeneous hydrogenation are more than ten years old [10]. Interest has been revived in the last few years largely for two reasons—the availability of a new generation of ligands which greatly extend the range of catalysis



Scheme 5

[11], and improved methodologies which permit computational chemistry to make realistic predictions about the catalytic cycle [12]. One of the frustrations of previous efforts was the observation of a late catalytic intermediate—a rhodium alkylhydride, without any access to its likely dihydride precursor. This raises the question as to whether the primary intermediate has sufficient lifetime in any case to permit direct observation (Scheme 5).

We were attracted to explore the problem further because of the report of catalysts based on the ligand Phanephos that are highly reactive at low temperatures [13], and also because of the new insights into reactive transients opened up by para-hydrogen NMR experiments [14,15]. Any successes derived through the application of this methodology to dehydroamino acid reductions will be reported.

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