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Organic Process Research & Development

Letter to the Editor

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Key Enantioselective Hydrogenation Steps in the Syntheses of Two Renin Inhibitors: Missing Origin and Incorrect Description

Dear Editor:

A group at Merck reported "A Practical Synthesis of Renin Inhibitor MK-1597 (ACT-178882) via Catalytic Enantioselective Hydrogenation and Epimerization of a Piperidine Intermediate",[1] and this was highlighted in your journal.[2] Another group at Merck later published a second paper entitled "Convergent Kilo-Scale Synthesis of a Potent Renin Inhibitor for the Treatment of Hypertension" in your journal.[3] The chiral cores of these compounds are identical and were both created "via a catalytic asymmetric hydrogenation of a tetrasubstituted ene−ester" using the same method.

I am obliged to write to you because (1) both groups omit mentioning that that method is an adaptation of the Firmenich enantioselective hydrogenation process for making the fragrance chemical (+)-*cis*-methyl dihydrojasmonate, and (2) the method—and how they arrived at it—is described in an incorrect manner in both papers and, hence, in your Highlights as well. Permit me to clarify the situation in as much detail as necessary rather than to just list our patents and publications.

At the time, the Firmenich team, that is, D. A. Dobbs, K. P. M. Vanhessche, E. Brazi, and I, at Firmenich, aided by J.-P. Genêt and J.-Y. Lenoir at the Ecole Nationale Supérieure de Chimie de Paris, and S. H. Bergens and J. Wiles at the University of Alberta, eventually confirmed that none of the methods available at the time could hydrogenate our substrate, a vinylogous β-oxoester incorporating a tetrasubstituted C=C bond. This was to be expected. An entirely new type of catalyst was needed. We hypothesized that very electrophilic dications $[Ru(P-P)(sol)_n]^{2+}$ in a weakly coordinating, aprotic solvent might do the trick. Active species of this type were unknown at the time and, to my knowledge, still are. We tried to generate such species by treating a 1:1 mixture of $[Ru(COD)(methallyl)_2]$ and various ligands P−P with 2 equiv of $HBF_4{\cdot}Et_2O$ in CH_2Cl_2. With tuning/screening of the ligands P−P, this idea worked, and the resulting "blind" recipe was patented.[4] We then identified the precatalyst obtained when using the ligand (−)-Me-DuPHOS, and the derived active catalyst that is formed on exposure to H_2 as well. The precatalyst turned out to be a hydridomonocation fluoborate $[Ru((-)\text{-Me-DuPHOS})(H)(COT)]BF_4$ (COT = 1,3,5-cyclooctatriene), and the catalyst is the derived $[Ru(P-P)(H)(sol)_n]BF_4$. The stoichiometry of the sequence that leads to this precatalyst requires 1 equiv $HBF_4{\cdot}Et_2O$, and we confirmed that complete conversion is achieved with 1 equiv and that the overall reaction is cleaner that way. This was also patented[5] and the entire story later published in the open literature.[6] We then devised a second method for generating the same kinds of precatalysts, starting out with the protonation of $[Ru(COD)(COT)]$, which allowed us to incorporate the ligands (−)-Me-DuPHOS, (+)-BINAP, (+)-Tol-BINAP, and (−)-JOSIPHOS in a transparent and controlled manner. There are structural variants depending on the ligand P−P. The active catalysts obtained from them are all of the type $[Ru(P-P)(H)(sol)_n]BF_4$. This was published in a second paper.[7] See Salzer et al. for a related approach.[8]

Previous work leading up to ours and previous reports on presumed dications and one authentic dication $[Ru(P-P)(sol)_n]^{2+}$ are fully discussed in our papers. Two groups (Bruneau et al.,[9] and Zhang et al.[10]) later used the recipe involving $[Ru(COD)(methallyl)_2]$ and 2 equiv $HBF_4{\cdot}Et_2O$ and quoted us but did not identify the precatalysts and catalysts they had in hand. Zhang et al. also used the subsequent epimerization step that is part of the Merck strategy.

Both of the Merck papers state that their "catalyst solution" was obtained upon adding ligand SL-J212-1 (a JOSIPHOS-type ligand; the provenance is not indicated) to $[Ru(COD)(methallyl)_2]$ in CH_2Cl_2 solution. This is incorrect, because (1) the precatalyst is formed upon exposure of this mixture to $HBF_4{\cdot}Et_2O$ and (2) the active catalyst is then formed upon exposure of the precatalyst to H_2; see above. The main text of paper I[1] and the entire paper II[3] do not at all refer to these two steps. Thus, paper I[1] says: "we were pleased that the Ru metal precursor $(COD)Ru(Me\text{-}allyl)_2$ and JOSIPHOS ligand SL-J212-1 gave >90% ee ...; see also Table 1"; only in one of two relevant sections in the Experimental Section in paper I is it described that "the catalyst solution ($[Ru(COD)(methallyl)_2]$ + ligand) was cooled ..., and $HBF_4{\cdot}Et_2O$ ... was added", to the amount of 1.9 equiv. This issue is further obscured by the fact that both substrates were subjected to hydrogenation in largely N-protonated form—which was generated by reaction with $HBF_4{\cdot}Et_2O$ (0.9 equiv in paper I,[1] 1.2 equiv in paper II[3]). It is conceivable that reaction of the SL-J212-1 + $[Ru(COD)(methallyl)_2]$ mixture with a small fraction of the protonated substrates also brings about the formation of the precatalyst—but this is also not mentioned. Note that the first step in the sequence that leads to the precatalysts is simply monoprotonation of the ligand P−P and that the known reaction between $[Ru(COD)(methallyl)_2]$ and the ligands P−P is negligibly slow under these conditions (see our first paper).

Finally, I must mention that an addition and correction of paper I[1] was recently published;[11] however, it does not refer to paper II,[3] nor does paper II refer to it.

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