Organic Process Research & Development

Letter to the Editor

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Response to the Comments by Rautenstrauch et al. on our Article, "Convergent Kilo-Scale Synthesis of a Potent Renin Inhibitor for the Treatment of Hypertension"

Dear Editor,

We acknowledge the Letter to the Editor from Valentin Rautenstrauch regarding our recent paper "Convergent Kilo-Scale Synthesis of a Potent Renin Inhibitor for the Treatment of Hypertension".[1] In this letter, the following two major concerns are raised: (1) that we omitted referring to seminal work on hydrogenation of tetrasubstituted olefins using Ru-based catalysts by Dr. Genet and Dr. Rautenstrauch and their co-workers[2] and (2) that the chiral hydrogenation used in our paper is described in an "incorrect manner". In this letter we specifically address these concerns as they pertain to our manuscript[1] only.

The development of the specific hydrogenation process was already described by another group in our company in *The Journal of Organic Chemistry* (JOC).[3] We did not believe that our manuscript was an appropriate forum for a discussion of known parameters which affect precatalyst formation or any specific mechanistic implications. Since the exact same ligand/metal/acid combination was used as a starting point for optimization in our hydrogenation, we believe that crediting this team with the development of this process for our substrate class was appropriate. However, we completely agree that there was an omission of the aforementioned citations which describe the discovery of these types of catalytic systems, and we sincerely apologize for this oversight. We were already in the process of preparing an addition and correction[4] to our manuscript to include this very important precedent. We only became aware of this error recently when our colleagues published an addition and correction[5] to their paper which appeared in JOC in early 2012.

We did, however, truthfully discuss the optimization of the initial result from the JOC publication[3] for our substrate. Contrary to the precedent from Dr. Genet's and Dr. Rautenstrauch's groups, we did not form the precatalyst by addition of $HBF_4{\cdot}OEt_2$ to the mixture of ligand and ruthenium prior to substrate addition. In our case, the mixture of ligand/Ru is added directly to the substrate which is already premixed with 1.2 equiv of $HBF_4{\cdot}OEt_2$ relative to substrate. Presumably, formation of the precatalyst occurs with the excess acid remaining (0.2 equiv relative to substrate and 13 equiv relative to the Ru/L loading) after protonation of the pyridine in the substrate. While not discussed in our paper, this procedure proved more reliable and convenient on scale-up and in addition avoids handling the more sensitive precatalytic species. In our paper[1] we refer to this premixed ligand and Ru complex solution as a "preformed catalyst" which, of course, is not mechanistically true, but a common euphemism used in transition metal catalysis (in much the same way that [$Pd(OAc)_2$ + ligand] is not the "active" catalyst in a Suzuki coupling). In our addition and correction,[4] we have altered the language to "premixed ligand/Ru solution" to eliminate any ambiguity. In any case, we assure you that our procedure, performed as described, does in fact provide the reported yield and enantioselectivity.

Best Regards,

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Notes

The authors declare no competing financial interest.

REFERENCES

(1) Campeau, L.-C.; Dolman, S. J.; Gavreau, D.; Corley, E.; Liu, J.; Guidry, E. N.; Ouellet, S. G.; Steinhuebel, D.; Weisel, M.; O'Shea, P. D.. *Org. Process Res. Dev.* **2011**, *15*, 1138.

(2) (a) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genet, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992. (b) Wiles, J. A.; Bergens, S. H.; Vanhessche, K. P. M.; Dobbs, D. A.; Rautenstrauch, V. *Angew. Chem., Int. Ed.* **2001**, *40*, 914, 1573. (c) Dupau, P.; Bruneau, C.; Dixneuf, P. H. *Adv. Synth. Catal.* **2001**, *343*, 331. (d) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570.

(3) Molinaro, C.; Shulz, S.; Roy, A.; Lau, S.; Trinh, T.; Angelaud, R.; O'Shea, P. D.; Abele, S.; Cameron, M.; Corley, E.; Funel, J.-A.; Steinhuebel, D.; Wiesel, M.; Krska, S. *J. Org. Chem.* **2011**, *76*, 1062.

(4) Campeau, L.-C.; Dolman, S. J.; Gavreau, D.; Corley, E.; Liu, J.; Guidry, E. N.; Ouellet, S. G.; Steinhuebel, D.; Weisel, M.; O'Shea, P. D.. *Org. Process Res. Dev.* **2012**, DOI: 10.0121/op300123u.

(5) Molinaro, C.; Shulz, S.; Roy, A.; Lau, S.; Trinh, T.; Angelaud, R.; O'Shea, P. D.; Abele, S.; Cameron, M.; Corley, E.; Funel, J.-A.; Steinhuebel, D.; Wiesel, M.; Krska, S. *J. Org. Chem.* **2012**, *77*, 813.

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