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Denisa Hidasová:

Asymmetric Tandem Lithium Amide Conjugate Addition/Radical Reactions and their Application in the Total Synthesis of Natural Products

The thesis addresses the problem of efficient and environmentally benign stereoselective vicinal functionalization of simple acrylate molecules via a combination of aza-Michael addition and radical oxygenation of the resulting intermediate, i.e., a one-pot construction C-N and C-O bonds. This approach was then extended to cyclization of suitable precursors, thereby paving an unorthodox avenue to quite complex structures in a simple manner.

The text is split into five chapters: Introduction, Aims, Results and Discussion, Experimental, and Conclusions, followed by literature references. The text reads well and is characterized by logical buildup. The experiments seem to have been done with care and the Experimental part is at a professional level with almost all the required details. There are minimum typos and the lab slang is entirely eliminated. The structures and schemes are excellent and the occasional use of color helps the reader considerably.

Chapter 1 – Introduction is concise but informative with key references provided. However, I do not agree with the use of the word "tandem", which dominates the text and is also featured in the thesis title. "Tandem" should be confined to processes occurring simultaneously, which is certainly not the case here, as inadvertently admitted by the author, saying "followed by". The only appropriate description of the processes dealt with here should be "domino reactions", as advocated by Lutz Tietze, Dieter Enders, and many others (see, e.g., the ERC "DominoCat" conference held in Aachen in 2015).
There are a few other minor issues:
p. 9, line 2 and elsewhere: the cyclization processes should be characterized as 5-*exo*-***trig*** and 6-*endo*-***trig***, as originally introduced by Baldwin, rather than as 5-*exo* and 6-*endo*.
p. 14 bottom: The widely used proline-derived organocatalysts, first developed by Hayashi and Jørgensen, should have been included in ref [65].
p. 15 bottom: The list of cyclization methods, including Hg(II) and I_2, should surely be extended to those catalyzed by Pd(II) (see, e.g., the review in *Chem. Eur. J.* **2015**, *21*, 36 and subsequent papers by Christina White and others).

Chapter 2 – Specific aims are ambitious and clearly stated.

Chapter 3 – Results and Discussion revolves around the Davies-type asymmetric aza-Michael addition of chiral amides to acrylates, followed by a radical α-oxygenation of the resulting intermediate enolates – both in inter- and intra-molecular versions. The results are then applied for the synthesis of kainic acid and other functional molecules with a pyrrolidine motif. The domino process of aza-Michael addition / oxygenation, where the enolate initially generated undergoes the SET oxygenation, has been clearly shown to be superior to that using a stepwise protocol. Furthermore, a catalytic procedure, employing ferrocene **1-6** as a catalyst in combination with the oxoiminium salt **1-9**$^+$ has been identified as an optimum. Here, **1-9**$^+$ first serves as an oxidant, converting ferrocene (**1-6**) into the ferrocenium **1-6**$^+$, which is the reactive catalyst, while it itself is reduced to TEMPO (**1-9**). The latter species then traps the radical cation generated from the reaction of

the aza-Michael enolate on action of **1-6**$^+$, giving rise to the required α-oxygenated product. The alternative stepwise scenario or that using the ferrocenium **1-6**$^+$ as the catalyst in combination with TEMPO, proved less efficient. The author should be praised for developing this methodology to its optimum.
p. 24 and 26: The role LiCl in the aza-Michael addition should be commented.
p. 30, Scheme 3.1.6: The final product **3-8** is obtained from **3-3i** on Pd-catalyzed hydrogenation. Since the starting molecule has three benzylic centers, the author should rationalize the selectivity, as two benzyls are removed, whereas the third one remains unscathed.
p. 32, 2nd paragraph, line 2, and Scheme 3.1.8: The aza-Michael addition (**3-1** + **3-2**) is assumed to generate the (*Z*)-enolate **3-10** (as a lithium chelate), whereas deprotonation of the isolated β-amino derivative **3-4** is portrayed as a process generating the (*E*)-isomer **3-12**. What is the rationale?
p. 33, Scheme 3.1.9 and elsewhere: The zinc reduction, although successful for the conversion of **3-15** into **3-16**, failed with **3-3b**. Would other methods, such as that employing the $Mo(CO)_6$, be of any use?
p. 36, Scheme 3.1.12: Formation of **3-35** is said to occur with a 10:1 *anti/syn* ratio, which presumably refers to the formation the α,β-centers. What is the relation to the residing δ-center – is it pure 100% as the Scheme seems to suggest?
p. 37, Scheme **3-3k**: it would be helpful to give the diastereoisomeric ratio in the starting compound **3-3k** and in the final product **3-41**. The final cyclization here, carried out with Bu^{t}OK, gave **3-41** in only 58% yield. Would, e.g., a Grignard reagent perform better?
p. 41, Scheme 3.2.5 and the paragraph underneath seems to be in conflict: Formula **3-51a** shows the *cis* configuration of the 3- and 4-substituents, which appears to be confirmed by the ORTEP diagram (Figure 3.2.1). However, *trans*-configuration referred to in the text.
p. 54, last line: What is the "*chair*-**3-80** transition state"? According to Scheme 3.2.14 (p. 55), there are two radical intermediates shown (not really transition states), named "*chair*-**3-80**" and "*boat*-**3-80**", which differ in the orientation of cyclopentene moiety. Since this intramolecular addition gives rise to a five-membered ring, I do not think the words "chair" or "boat" can be used to describe the transition states, as these are reserved for the six-membered rings, whereas different nomenclature is used for five-membered rings. Perhaps, *re/si* notation could be used instead for the description of the radical addition to the double bond of the two rotamers.
p. 55, Scheme 3.2.14: in formulae **3-74** and **3-75** the use of the dotted and wedged bonds is in violation of the IUPAC rules.
p. 57, Scheme 3.2.16: If **3-59a** is a 6:1 mixture of diastereoisomers and one that is *cis*-configured is cyclized to produce lactone **3-86** (9%), while the other that does not undergo cyclization (**3-85**), it should be *trans*-configured by default and that should be indicated in the formulae. Or do I miss something here? Further, I do not quite understand the NOE argument, where comparison is made with **3-65**. Notably, in five-membered rings, the NMR results may not be as reliable as in their six-membered congeners (personal experience). Anyway, in line 4 from the bottom, the text "compounds **3-58** and **3-65**…" is confusing, since **3-58** is actually methyl cyclohex-1-ene-1-carboxylate (Scheme 3.2.10, p. 48).
p. 60, Scheme 3.2.18: The use of the dotted and wedged lines in most of the formulae violates the IUPAC rules.
p. 60, last line: What is "insufficient deprotonation of pyrrolidines **3-94**"?
p. 63, Scheme 3.2.23: Formula **3-106** violates the IUPAC rules again.

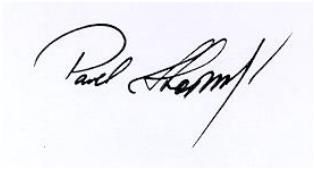
Chapter 4 – Experimental Section is professional with only a few minor issues: (1) the amount of silica gel used for column chromatography is never mentioned. (2) Giving the yields of products after chromatography is OK but when the product was further crystallized, the yield after crystallization should also be given. (3) For known compounds there should be comparison of mp and $[\alpha]_D$ with those published in the literature. (4) For successful chromatographic separation it should be stated in which order the compounds were eluted from the column (it may not always correspond to their TLC behavior). (5) For crystalline compounds, whose melting points are given, the author should state the solvent that was used for the crystallization. Or were these just solidified products after evaporation of the chromatographic fraction? (6) Stating the solvent employed for obtaining crystals suitable for X-ray analysis is an absolute must; I could not find this information - neither in the Experimental, nor in the Tables on pp 173 and 174.

Chapter 5 – Conclusions are succinct and sound. The candidate has emphasized, quite rightly, the efficiency of this green methodology, which allows a straightforward approach to molecules that are difficult to construct.

Minor formal points

p. 6, line 5 from the bottom (relating to Scheme 1.3): Compound **1-4** is an enol, rather than a "neutral carbonyl compound".
p. 6, legend to Scheme 1.3 should read "α-carbon**y**l radical" rather than "carbonal".
p. 16, Scheme 1.13: The top formula should be a cation (tetravalent nitrogen).
p. 27, second paragraph: reference to the absolute configuration of the product of the aza-Michael addition should be given.
p. 30, line 3/4 from bottom: "have *syn*-configuration" is a rather clumsy expression and should read, e.g., "is *syn*-configured".
p. 33, 2nd paragraph, line 1: "reverse threonine derivative *anti*-**3-3b**" is a rather clumsy expression of the fact that this is a threonine isomer (both positional and stereochemical).
p. 36, line 9: "Deprotection of the … protecting group" is rather amusing; it should read, e.g., "Removal of the … protecting group".
p. 62: "The diastereoselectivity of products…" Note that products cannot have diastereoselectivity.
p. 63, line 3 should read "**non**-selectivity" rather than "*un*selectivity".
Other than these, there are occasions of missing articles (a, the) but this is quite common for non-native speakers.

Overall: The candidate has clearly demonstrated her ability to carry out high-quality research and to write about it; she should be proud of her achievements. Particularly refreshing is the mechanistic insight, which helped to optimize the method and expand its scope, and eventually allowed the synthesis of several "real molecules". The candidate has emphasized, quite rightly, the efficiency of the combination of ferrocene (**1-6**) with the *N*-oxoiminium salt **1-9**$^+$, which is superior to the reciprocal version employing the ferrocenium (**1-6**$^+$) and TEMPO (**1-9**). I had the opportunity to monitor the progress of the project by attending the candidate's various presentations, so that I know what I am talking about. The meticulous planning of the experiments, mostly aided by model studies, can serve as a great example to her colleagues and followers. This work will undoubtedly serve as an inspiration to synthetic organic chemists world-wide. I have no reservations and recommend that the candidate be awarded a **PhD**. Well done.



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