The Combination of Anionic and Radical Reactions to Oxidative Tandem Processes Exemplified by the Synthesis of Functionalized Pyrrolidines

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Received February 16, 2000

The design of domino or tandem processes is one of the most attractive areas of organic research.[1] So far, most of the sequential strategies involve intermediates of the same oxidation state. Naturally, this leads to limitations due to the inherent reactivity patterns of these intermediates. The most appealing way to overcome this problem and to open new reaction channels are strategies that allow the selective change of the oxidation state of intermediates during reaction sequences by electron transfer.[2] For reductive tandem processes, SmI_2[3] has proven a valuable reagent. On the other hand, oxidative reaction sequences incorporating anionic and radical reaction steps are hardly explored.[4]

We report the combination of anionic and radical reactions to oxidative tandem processes, exemplified by lithium amide conjugate addition/SET/radical 5-exo cyclization/radical trapping. Since neither alternative intermolecular aminyl radical additions to α,β-unsaturated carbonyl compounds nor alkali enolate additions to alkenes are feasible reaction types, the results presented here provide a unique solution to reactivity limitations of different intermediate types.

A brief initial study of the conjugate addition of lithium *N*-allylamides **2a**−**c** to *tert*-butyl enoates **1a,b**[5] showed that *N*-allyl-β-amino esters **4aa**−**4bb** were formed via **3** at −78 °C in THF in good yields (Scheme 1).

The tandem lithium amide conjugate addition/radical 5-exo cyclization reactions were performed with ferrocenium hexafluorophosphate **5** as SET oxidant[6] for the β-amino enolate **3** (Scheme 1). For the termination of the reaction sequence, free radical TEMPO **6** was added since it reacts more slowly with α-carbonyl radicals **7** than with alkyl radicals **8** and oxygenated products are obtained, which provide ample opportunities for further transformations.

The reaction sequences of enoates **1a,b** and lithium *N*-allylamides **2a**−**c** in THF gave only two of the four possible pyrrolidine diastereomers **9aa**−**bb** with complete 2,3-*trans*-selectivity in good to high yield (Table 1). *tert*-Butyl cinnamate **1a** provided a higher yield of **9aa** or **9ab** in the presence of HMPA without influencing the cyclization diastereoselectivity (entries 2,5 vs 1,3). DME as the solvent yielded the cyclized product **9ab** in comparable yield (entry 4). With lithium amides **2a,c**, essentially no cyclization diastereoselectivity to **9aa,ac** was observed

Scheme 1. Tandem Lithium Amide Conjugate Addition/Radical 5-exo Cyclization to Pyrrolidines **9**, Mediated by **5**/**6**

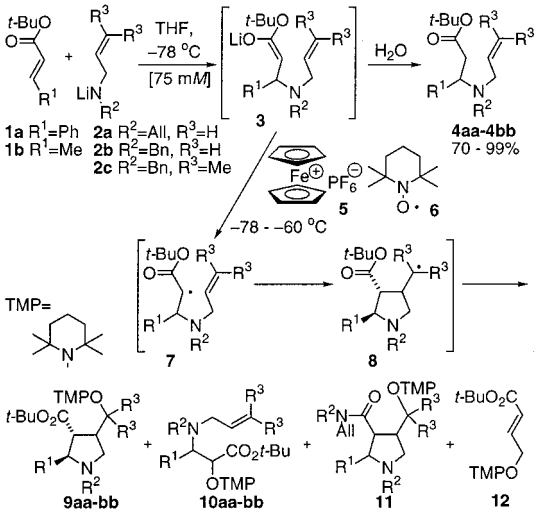

Table 1. Tandem Lithium Amide Conjugate Addition/Radical 5-exo Cyclizations to Pyrrolidines **9**

entry	1	2	**9** (%, *3,4-cis*/*trans*)	**10** (%)	**4** (%)	other (%)
1	**a**	**a**	**aa** (67, 1.2:1)	4		**11aa** (8)
2	**a**	**a**[a]	**aa** (85, 1.3:1)			**11aa** (4)
3	**a**	**b**	**ab** (47, 4.9:1)	12	20	
4	**a**	**b**[b]	**ab** (63, 7.2:1)	11	5	
5	**a**	**b**[a]	**ab** (68, 5.8:1)	12	10	
6	**a**	**c**	**ac** (76, 1:1.1)	13	8	
7	**a**	**c**[a]	**ac** (69, 1:1)	11	11	
8	**b**	**a**	**ba** (51, 1:2.4)	5		**12** (3)
9	**b**	**a**[a]	**ba** (25, 1:1.5)			**12** (54)
10	**b**	**a**[c]	**ba** (53, 1:1.6)	4		**12** (6)
11	**b**	**b**	**bb** (56, 4.5:1)	18	9	**12** (5)

[a] Reaction sequence in 11 mL of THF/2.5 mL of HMPA. [b] DME as solvent. [c] Temperature for oxidative cyclization −45 °C.

(entries 1,2,6,7). On the other hand, the more biased lithium amide **2b** gave a >4.9:1 3,4-*cis*-selectivity in **9ab** (entries 3−5).

tert-Butyl crotonate **1b** gave the pyrrolidine derivatives **9ba** and **9bb** in acceptable yields (entries 8−11).[7] HMPA had a detrimental effect on the yield of **9ba**, since γ-deprotonation leading finally to **12** competes with conjugate addition (entry 9). The stereochemical outcome depended on the lithium amide. The reaction sequence of **1b**/**2a** gave the 3,4-*trans*-pyrrolidine **9ba** preferentially at −78 °C (entry 8), but the selectivity decreased if the temperature was raised to −45 °C (entry 10). With **2b**, the 3,4-*cis*-pyrrolidine **9bb** was formed with a 4.5:1 selectivity (entry 11). From the reactions, small amounts of the conjugate addition products **4**, acyclic TEMPO trapping products **10**, and pyrrolidinecarboxamides **11** were isolated. To minimize the formation of **10**, a mixture of **5** and **6** was added in all reactions except for the synthesis of **9ac** where TEMPO **6** was added before **5** to avoid oxidation of the cyclized tertiary radical **8ac** to a carbenium ion. The configuration of **9** was assigned on the basis of NOE experiments and chemical transformations (vide infra).

The efficiency of the tandem process was compared to a stepwise procedure. Deprotonation of β-amino esters **4aa** or **4ba** with LDA and oxidative cyclization by **5** in the presence of TEMPO **6** gave pyrrolidines **9aa** or **9ba** in 66 and 64% yield (Scheme 2). While the overall yield of the two-step methodology was only slightly lower than that of the tandem reactions (59 vs

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(2) Review on electron transfer-induced reactions: Dalko, P. I. *Tetrahedron* **1995**, *51*, 7579.
(3) Review: Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.
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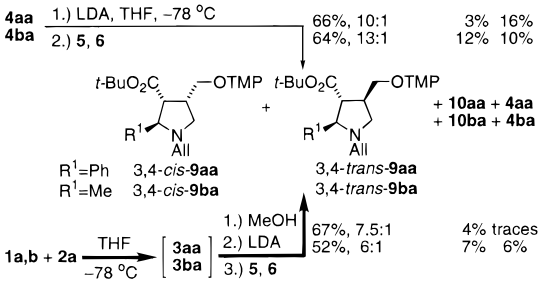
(6) For the use of **5**,**6**, see: (a) Jahn, U.; Hartmann, P. *Chem. Commun.* **1998**, 209. (b) Jahn, U. *J. Org. Chem.* **1998**, *63*, 7130 and references therein.

(7) Although the overall yields are only in the 50% range for **1b**, the average yield of each sequence step from **2** is at least 88%.

10.1021/ja000565v CCC: $19.00
Published on Web 05/13/2000

Scheme 2. Cyclizations of β-Amino Esters **4** and the Development of a *cis*-Selective Tandem Addition/Cyclization



67% for **9aa**, 46 vs 51% for **9ba**), the cyclization diastereoselectivity changed dramatically, now providing the 3,4-*cis* isomer in a >10:1 ratio!

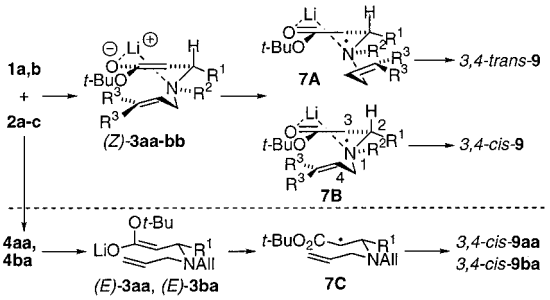
This control element can be incorporated favorably into the tandem reactions described above by inserting a protonation/deprotonation step after conjugate addition. Thus, pyrrolidines **9aa** and **9ba** can now be obtained with preferred 3,4-*cis*-stereoselectivity from **1a,b**/**2a** (Scheme 2).

Enolate geometry most likely determines the contrasting radical cyclization diastereoselectivities. Therefore, enolates **3ba** derived from conjugate addition of **2a** to **1b** and from deprotonation of **4ba** with LDA were trapped as silyl ketene acetals (Supporting Information). The conjugate addition derived enolate **3ba** possesses *(Z)*-configuration, while deprotonation of β-amino ester **4ba** gives *(E)*-enolate **3ba** with a selectivity of 14:1 as determined by NOE experiments.[8]

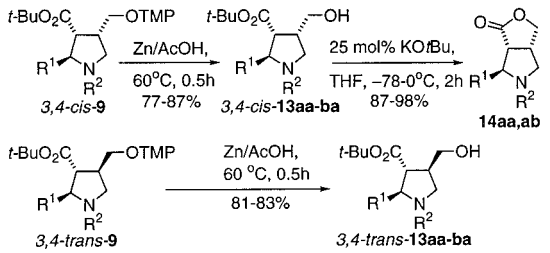
As a working hypothesis, enolate *(Z)*-**3ba** most likely exists as a chelate that is not broken immediately after oxidation to radical **7A** or 7**B** (Scheme 3).[9] For 3,4-*trans*-**9ba**, the cyclizing *N*-allyl group is preferentially oriented toward the less demanding C^2-substituent as in **7A**. Increasing steric requirements in the 1-, 2-, and 4-positions offer a more favorable orientation of the cyclizing *N*-allyl group toward the ester group in transition state **7B** leading to the 3,4-*cis* isomer (entries 8 vs 1,3,6,11). On the other hand, enolates *(E)*-**3aa,ba** cannot chelate and the derived radicals **7C** cyclize according to a Beckwith−Houk open transition state[10] with the enolate geometry of **3aa**, **3ba** probably preserved in the α-ester radical **7C** due to its notable rotational barrier.[11]

To aid configuration assignment, the tetramethylpiperidinyl group was cleaved in the presence of the *tert*-butyl ester and the

Scheme 3. Rationalization of the Cyclization Diastereoselectivity



Scheme 4. Configuration Assignment of Pyrrolidines **7** by Deprotection(/Lactonization)



N-protecting groups with Zn/AcOH[6] to alcohols **13aa-ba** in good yields (Scheme 4). Addition of catalytic KO*t*Bu to 3,4-*cis*-**13aa-ba** induced lactonization to **14** in almost quantitative yield while 3,4-*trans*-**13aa-ba** remained unaffected.

In summary, we have shown that oxidative anion/radical reaction sequences, exemplified by lithium amide conjugate addition/SET oxidation/radical 5-exo cyclization, are an attractive strategy to obtain highly functionalized pyrrolidines in a single operation from very simple precursors. The study shows clearly, that the stereochemical information of enolates can be translated into the radical cyclizations. Further detailed investigations are necessary to generalize this new control element for radical chemistry. The tandem reaction results indicate that this strategy should be general as other anionic 1,4-additions may form the basis for similar reaction cascades.

Acknowledgment. We thank the DFG and the Fonds der Chemischen Industrie for funding. Professor H. Hopf's support and interest in this project is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of compounds **4, 9**−**14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA000565V

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