

Samarium (II) Iodide-Mediated Intramolecular Reductive Coupling of Aldehydes with Allenic Esters

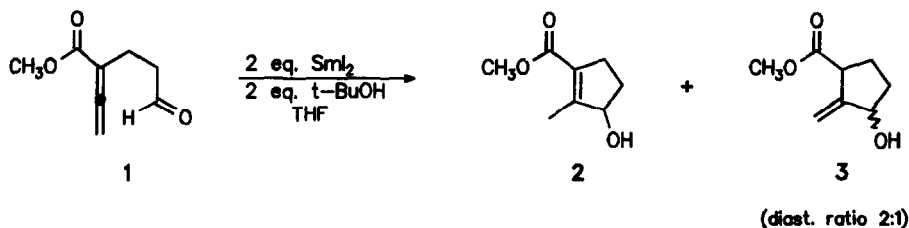
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Abstract: Ester-substituted allenic aldehydes **1**, **4**, **6a**, and **6b** undergo reductive cyclizations when treated with SmI_2 . These conversions are completely regioselective and in the case of **4** occur with high diastereoselectivity. Product formation is crucially dependent on the choice of solvent and proton source.

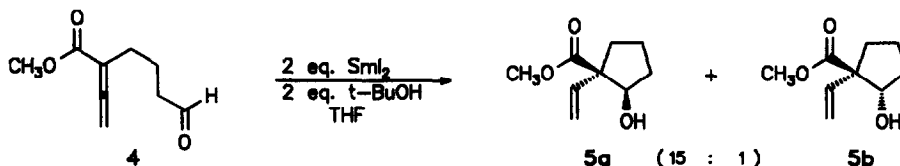
Radical cyclization reactions have proven to be an efficient means for the construction of carbo- and heterocyclic frameworks. While olefins and acetylenes have been widely employed in such processes, related studies of allenes are still scarce.¹ In this particular field, investigations of alkyl substituted derivatives were by far predominating. The cyclization behavior of electron-deficient allenes, however, was addressed only once.^{1d} As part of our general interest in the chemistry of allenes, we turned our attention to the samarium (II) iodide-mediated intramolecular reductive coupling reaction between allenic esters and the carbonyl group of aldehydes. Although that type of transformation was investigated with olefinic² and acetylenic³ α,β -unsaturated esters, no systematic study dealing with allenic esters has appeared.

When a 0.2M THF-solution of allenic aldehyde **1**⁴ in the presence of *t*-butanol at room temperature was treated dropwise with 0.1M SmI_2 -solution in THF, the reducing agent was rapidly decolorized until 2 equivalents were consumed. After workup,⁵ not surprisingly, a mixture of products was isolated in 66% combined yield originating from C-C-bond formation between the central allenic carbon and the aldehyde moiety (Scheme 1). The endocyclic isomer **2** was favored over the diastereomers **3** by 2:1.



Scheme 1

By contrast, extension of the aldehyde-containing side chain by one carbon resulted in a regiochemical change. Under analogous conditions,⁵ ring closure of **4** occurred selectively via the proximal sp^2 -carbon (Scheme 2) leading to vinylcyclopentanois **5a** and **5b**⁶ in 82% yield and in the notable diastereomeric ratio⁷ of 15:1.



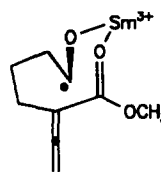
Scheme 2

The *cis*-orientation of the ester and hydroxyl functions in the major diastereomer **5a** was revealed by NOE-difference spectroscopy. Upon irradiation at the resonance of 2-H an enhancement of the vinyl- H_α signal was recorded for **5a**, whereas the corresponding protons in **5b** remained unaffected under these conditions.

Assuming the reaction mechanism to involve primary electron transfer to the aldehyde carbonyl generating a ketyl radical which would subsequently add to the allene π -system, the regiochemical outcome of the above cyclization is unexpected. For electronic reasons, ketyl radicals, being nucleophilic in character should prefer the sp -center as the most electrophilic reaction site within the allene. This is exactly what Crandall^{1d} found in his investigation of the cyclization behavior of alkyl radicals which, in accord with their nucleophilic properties, were found to add exclusively to the sp -carbon of electron-deficient allenes, forming the corresponding six-membered rather than the five-membered rings.

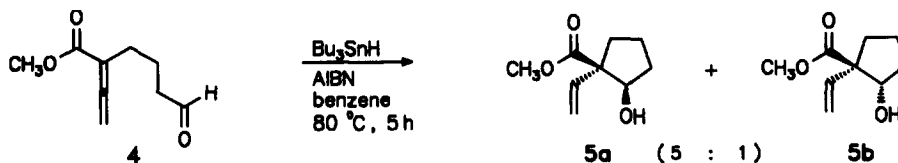
While our results in terms of regiochemistry could well be due to some other mechanism being operative,⁸ the high diastereoselectivity of the transformation suggested a participation of the metal in a chelate between the ester and the developing hydroxyl function (Fig 1).

Figure 1



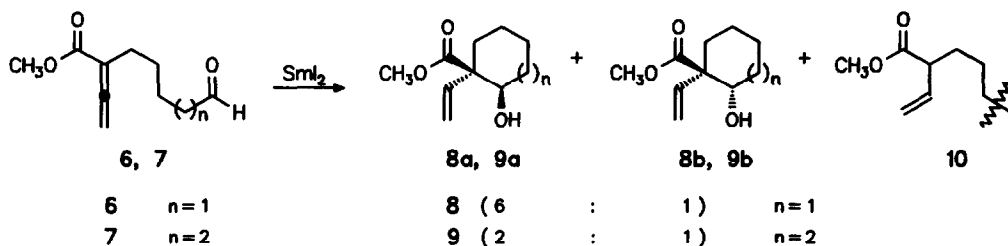
The stereochemical implications of the samarium ion's propensity to coordinate to oxygen ligands are well documented.⁹ Recently Inanaga¹⁰, in a study of an intramolecular Reformatsky reaction mediated by SmI_2 , considered a similar chelation to be the driving force on the way to medium-sized rings.

In this context, we wondered whether replacing SmI_2 by Bu_3SnH would result in lower stereoselectivity. This question was also of practical interest to us to circumvent the inconvenience of isolating the minor diastereomer **5b** out of a 15:1 mixture on a preparative scale. Enholm¹¹ has demonstrated the tin hydride reagent to be an effective promoter of intramolecular reductive cyclizations of unsaturated aldehydes and ketones. Compared to the corresponding SmI_2 -mediated process,^{2a} however, the stereoselectivity using Bu_3SnH was negligible. Not surprisingly so, when a 0.1M solution of **4** in benzene was heated in the presence of $\text{Bu}_3\text{SnH}/\text{AIBN}$ (1.5 eq./0.01 eq.), the desired diastereomers **5a** and **5b** were obtained in a 5:1 ratio in 37% yield (Scheme 3).



Scheme 3

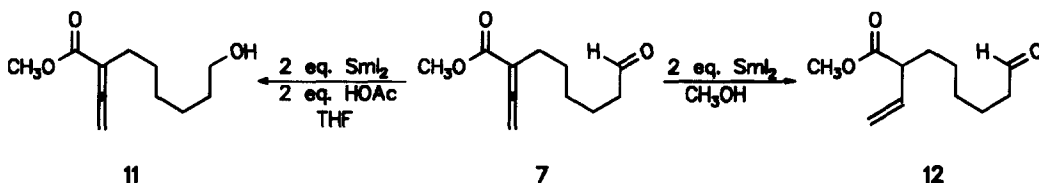
Exposure of the homologous aldehyde **6** (Scheme 4) to the conditions applied to the transformation in Scheme 2 lead in part to undesired conjugate reduction products **10**.¹² By use of methanol instead of *t*-butanol as a proton source, however, this pathway could be avoided and a clean formation of the six-membered ring alcohols **8a** and **8b**.¹³ was observed in 78% combined yield (diastereomeric ratio 6:1).⁷



Scheme 4

Attempts to prepare the seven-membered ring analogues **9a/9b** met with limited success, conjugate reduction being a competitive process that could not be completely suppressed. We found the highest preference of cyclized vs. uncyclized products in acetonitrile containing 10 eq. of water; the diastereoselectivity⁷ decreased to only 2:1.

Trying to improve the reaction conditions for the generation of the seven-membered rings, we reasoned that an increase in the acidity of the proton source might be favorable. Consequently, we conducted an experiment in the presence of two equivalents of acetic acid. While SmI_2 was rapidly consumed, no cyclized products were, however, generated. Instead, a clean reduction of the aldehyde function occurred to afford the primary alcohol **11** in 85% yield (Scheme 5).



Scheme 5

Finally, in continuation of our efforts to induce ring closure of **7**, we came across another striking example of the lanthanide reagent's ability to chemoselectively differentiate between the two reducible functionalities. Though again no cyclization was observed when the allene **7** was dissolved in methanol and treated with SmI_2 in THF, we were nevertheless pleased to find the α,β -unsaturated double bond to be reduced this time, product **12** being formed with the aldehyde functionality intact (Scheme 5).

We are currently investigating the potential generality of these chemoselective processes. Studies directed toward reductive couplings of allenic ketones are also underway.

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References and Notes

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- The requisite allenic esters were prepared by a slight modification (the reaction did proceed in the absence of boron trifluoride etherate) of a literature procedure: Myrbohn, B.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 1100-1102.
- All reactions were conducted at ambient temperature employing a 0.2 M solution of substrate in THF (acetonitrile was used for the cyclization of **7**) containing the indicated equivalents of a proton donor. After 0.1M solution of SmI₂ was added dropwise, the reaction mixture was quenched with 10% sodium bicarbonate solution and extracted with ether. The crude was then subjected to flash chromatography, followed by HPLC, when necessary.
- NMR-Data (¹H at 400 MHz, ¹³C at 100 MHz; CDCl₃):
5a: δ_H 5.84 (dd, *J*=17.4, 10.7; 1H; CH=CH₂), 5.22 (dd, *J*=17.4, 0.6; 1H; CH=CH₂), 5.19 (dd, *J*=10.7, 0.6; 1H; CH=CH₂), 4.21 (m; 1H; 2-H), 3.73 (s; 3H; OCH₃), 3.01 (d, *J*=4.4; 1H; OH), 2.30-2.22 (m; 1H), 1.99-1.81 (m; 3H), 1.72-1.60 (m; 2H); δ_C 174.9, 137.8, 115.8, 78.8, 61.5, 52.0, 31.2, 30.1, 20.3.
5b: δ_H 6.10 (dd, *J*=17.5, 10.9; 1H; CH=CH₂), 5.33 (dd, *J*=10.9, 0.9; 1H; CH=CH₂), 5.25 (dd, *J*=17.5, 0.9; 1H; CH=CH₂), 4.39 (m; 1H; 2-H), 3.72 (s; 3H; OCH₃), 2.18-1.91 (m; 4H), 1.84-1.73 (m; 1H), 1.71-1.60 (m; 2H); δ_C 175.2, 135.3, 117.4, 82.9, 60.3, 52.2, 30.8, 29.7, 19.2.
8a: δ_H 5.98 (dd, *J*=17.6, 11.0; 1H; CH=CH₂), 5.23 (dd, *J*=11.0, 1.0; 1H; CH=CH₂), 5.18 (dd, *J*=17.6, 1.0; 1H; CH=CH₂), 3.75 (s; 3H; OCH₃), 3.63 (dd, *J*=9.2, 3.3; 1H, 2-H), 2.25-2.18 (m; 1H), 1.92-1.84 (m; 1H), 1.74-1.66 (m; 1H), 1.61-1.22 (m; 6H); δ_C 175.7, 139.2, 116.0, 74.2, 54.7, 52.0, 31.7, 31.5, 23.1, 22.3.
8b: δ_H 6.07 (dd, *J*=18.0, 11.0; 1H; CH=CH₂), 5.39 (dd, *J*=11.0, 1.1; 1H; CH=CH₂), 5.31 (dd, *J*=18.0, 1.1; 1H; CH=CH₂), 4.02 (dd, *J*=9.5, 3.7; 1H; 2-H), 3.72 (s; 3H; OCH₃), 2.12 (dt, *J*= 13.6, 4.0; 1H), 1.77-1.25 (m; 8H); δ_C 176.1, 135.2, 118.3, 72.1, 53.8, 52.2, 30.1, 29.4, 23.0, 21.3.
- Diastereomeric ratios were determined by integration of the vinyl-H_α signals in the 400 MHz ¹H-NMR spectra.
- Primary electron transfer to the allenic π-system followed by addition of the resulting reactive intermediate onto the aldehyde carbonyl, is a conceivable alternative.
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- These were identified in respect to their partial structure of an α-substituted β,γ-unsaturated ester, but not characterized any further.
- Relative stereochemistry was assigned to these diastereomers by comparison of the resonances of 2-H (3.63 ppm for **8a** vs. 4.02 ppm for **8b**) with those of similar compounds reported by Frater and Seebach: (a) Frater, G. *Helv.Chim. Acta* **1980**, *63*, 1383-1390, (b) Herradon, B.; Seebach, D. *Helv.Chim. Acta* **1989**, *72*, 690-714.

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