ORGANIC LETTERS

2010
Vol. 12, No. 18
4082−4085

SmI_2-Mediated 3-*exo-trig* Cyclization of β,γ-Unsaturated Carbonyl Compounds: Diastereoselective Synthesis of Cyclopropanols

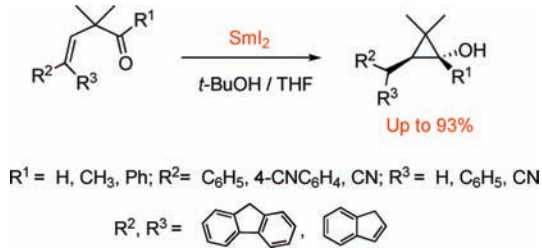
Mar Martin-Fontecha, Antonia R. Agarrabeitia, Maria J. Ortiz,* and Diego Armesto*

Departamento de Quimica Organica I, Facultad de Ciencias Quimicas, Universidad Complutense, 28040 Madrid, Spain

darmesto@quim.ucm.es; mjortiz@quim.ucm.es

Received July 19, 2010

ABSTRACT



SmI_2-mediated 3-*exo-trig* cyclizations of β,γ-unsaturated carbonyl compounds to generate cyclopropanols are not generally observed processes. The reported examples are limited to β,γ-unsaturated carbonyl compounds that possess ester groups conjugated with the alkene unit. The results of the current study show that this cyclization also occurs when other substitution patterns are present on the alkene moiety, affording (*E*)-cyclopropanols in good to excellent yields and in most cases with high degrees of diastereoselectivity.

A few years ago we reported the influence of electron-donor sensitizers on the single-electron transfer (SET)-promoted photochemical reactivity of β,γ-unsaturated aldehydes **1**, **2**, and **3** (Figure 1).[1] These compounds undergo photochemical oxa-di-π-methane rearrangement (ODPM), using 1,4-dimethoxynaphthalene as sensitizer, to afford the corresponding cyclopropyl aldehydes **4**, **5**, and **6**, respectively, in addition to products resulting from decarbonylation reactions. As such, they represented the first examples of ODPM reactions taking place via radical-anion intermediates.[1] In this effort, we observed that irradiation of aldehyde **3**, using *N*,*N*-dimethylaniline as an SET sensitizer, affords a variety of products including the cyclopropanol **7**. A mechanism involving a 3-*exo-trig* cyclization of a ketyl radical-anion intermediate was proposed to account for this diastereoselective process. The involvement of this intermediate was confirmed by the observation that reaction of **3** with SmI_2 in *t*-BuOH/THF results in formation of the (*E*)-cyclopropanol **7** in 61% yield.

This finding is interesting because carbonyl-alkene reductive coupling, using SmI_2 as a single-electron reducing agent, has been extensively employed in intermolecular and intramolecular C−C bond-forming reactions.[2] The latter reactions have been

(1) Armesto, D.; Ortiz, M. J.; Agarrabeitia, A. R.; Martin-Fontecha, M. *Org. Lett.* **2004**, *6*, 2261–2264.

(2) For selected reviews of SmI_2-mediated carbonyl-alkene reactions, see: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. (b) Skrydstrup, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 345–347. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354. (d) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777. (e) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751. (f) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (g) Edmonds, D. J.; Johnston, D.; Procter, D.-J. *Chem. Rev.* **2004**, *104*, 3371–3403. (h) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637. (i) Rudkin, I. M.; Miller, L. C.; Procter, D. *J. Organomet. Chem.* **2008**, *34*, 19–45. (j) Nicolau, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (k) Procter, D. J.; Flowers, R. A. Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry: London, 2010; Chapter 5.

10.1021/ol101666m
Published on Web 08/13/2010

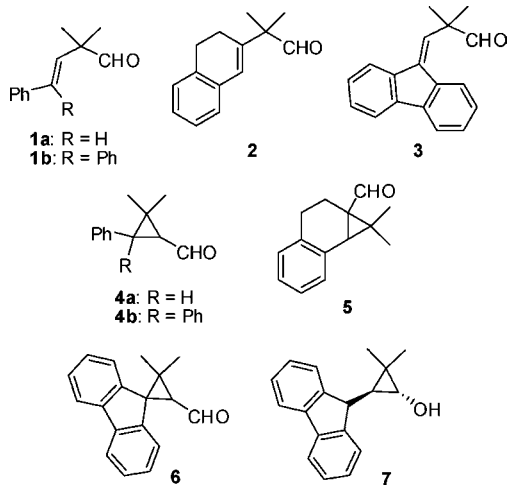
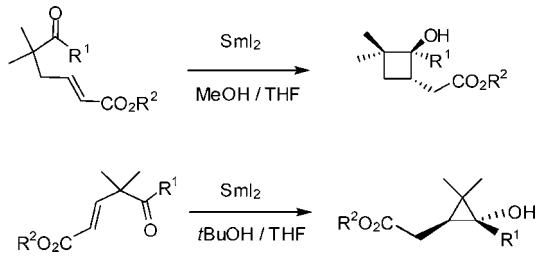


Figure 1. Starting aldehydes (**1**−**3**) and photoproducts (**4**−**7**) from our previous study.[1]

studied extensively by Molander and co-workers, who demonstrated that the SmI_2-mediated cyclization of ω-unsaturated carbonyl compounds in the presence of an alcohol as proton source in THF produces cyclopentanols, cyclohexanols, and cyclooctanols in good yields and with high degrees of stereoselectivity.[3] The process is general since both aldehydes and ketones can be used as coupling partners with both activated and unactivated alkenes. More recently, this method was applied to the synthesis of nine-, ten-, and eleven-membered carbocycles.[4]

However, to date formation of 4- or 3-membered rings by using this method is limited to substrates that contain ester-activated alkenes, as exemplified by the cyclobutanol-[5] and cyclopropanol-forming[6] reactions shown in Scheme 1.

Scheme 1. Previously Reported SmI_2-Mediated Carbonyl-Alkene Cyclization To Form Cyclobutanols[5] and Cyclopropanols[6]

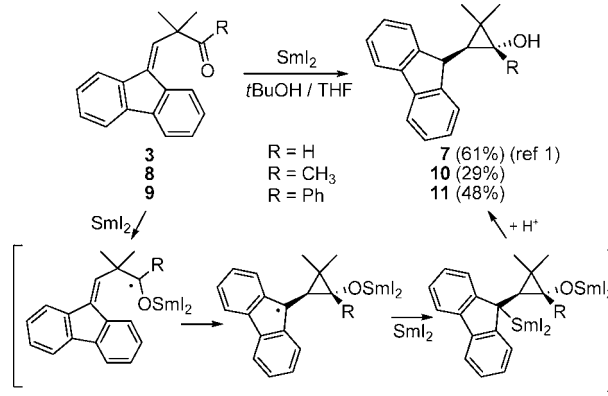


Nevertheless, the reaction of **3** with SmI_2 that affords cyclopropanol **7** in good yield suggests that other β,γ-unsaturated carbonyl compounds, not containing ester-activated alkene moieties, could participate in 3-*exo*-*trig* cyclizations to generate cyclopropanols.

(3) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132–3139. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186–3192. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872–882.
(4) Saadi, J.; Lentz, D.; Reissig, H.-U. *Org. Lett.* **2009**, *11*, 3334–3337.
(5) Edmons, D. J.; Kenneth, W. M.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190–3198, and references therein.

To explore this possibility, we have extended the study to include the methyl and phenyl ketones **8** and **9** that are structurally related to aldehyde **3**. Treatment of these substrates with SmI_2, under the same conditions used for aldehyde **3**, leads to exclusive formation of the corresponding (*E*)-cyclopropanols **10** and **11** in 29% and 48% yield, respectively (Scheme 2). A conventional mechanism is proposed to account for these cyclization reactions (Scheme 2).

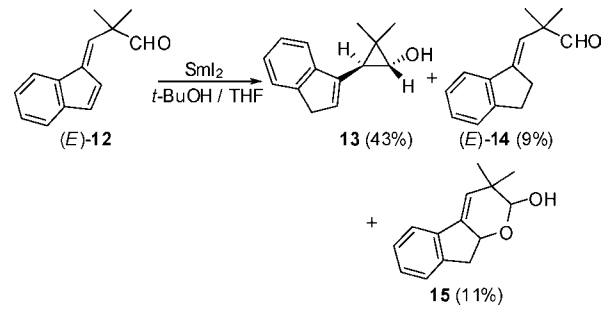
Scheme 2. SmI_2-Mediated 3-*exo*-*trig* Cyclization of Fluorene Derivatives **3**, **8**, and **9**



The stereochemistry of the products of these reactions was determined by using 1D NOESY experiments (see Supporting Information). In each case, the stereochemical outcome matches those observed in the formation of five- to seven-membered cycloalkanols by using this method and that has been attributed to a stereoelectronically driven strong preference for an antiparallel relationship of the ketyl radical and the alkene moiety.[3]

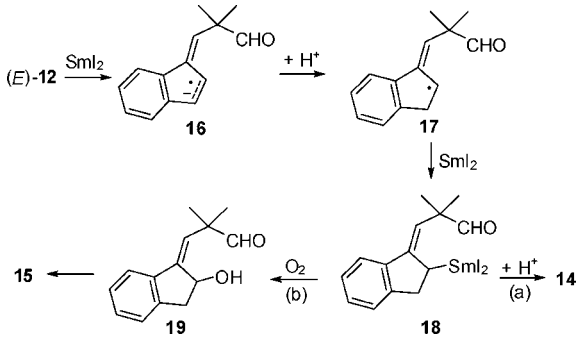
To evaluate whether other unactivated β,γ-unsaturated carbonyl compounds also undergo the 3-*exo*-*trig* cyclization, the reactivity of aldehyde (*E*)-**12** was examined. Indeed, reaction of (*E*)-**12** with SmI_2 leads to formation of the corresponding (*E*)-cyclopropanol **13** in 43% yield. This finding demonstrates that this process is not limited to fluorene derivatives. Moreover, two new substances, identified as aldehyde **14** and cyclic hemiacetal **15**, were also generated in this reaction in 9% and 11% yield, respectively (Scheme 3).

Scheme 3. Treatment of Aldehyde **12** with SmI_2



Possible mechanistic pathways for formation of **14** and **15** involve the intermediacy of the radical-anion **16**, which generates radical **17** by protonation. Reduction of **17** by a second molecule of SmI_2, followed by protonation of the samarium derivative **18**, affords aldehyde **14** (Scheme 4, path a).

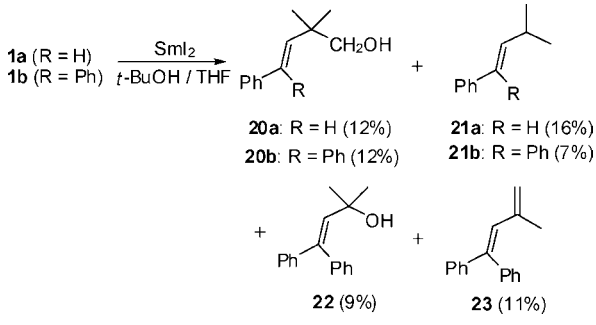
Scheme 4



Alternatively, oxidation of **18** by nucleophilic addition of molecular oxygen generates the δ-hydroxyaldehyde **19**, which undergoes intramolecular cyclization to **15** (Scheme 4, path b). This mechanistic hypothesis is supported by the results of previously described reactions of organosamarium species with molecular oxygen.[3a]

To explore the scope of the 3-*exo*-*trig* cyclization, the study was extended to include simple acyclic aldehydes **1**, with monophenyl and diphenyl substitution on the double bond. However, treatment of aldehyde (*E*)-**1a** with SmI_2 does not provide the expected cyclopropanol but rather yields alcohol (*E*)-**20a** (12%), resulting from direct reduction of the carbonyl group, along with the alkene (*E*)-**21a** (16%) (Scheme 5). Similarly, aldehyde **1b** affords alcohol **20b** and

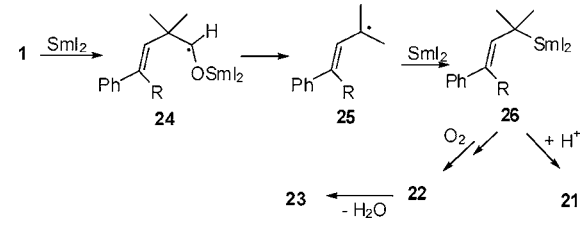
Scheme 5. Treatment of Aldehydes **1** with SmI_2



alkene **21b** in 12% and 7% yield, respectively, in addition to the tertiary alcohol **22** (9%) and the 1,3-diene **23** (11%) when treated with SmI_2.

The formation of alkenes **21** in this process is consistent with the involvement of the alkylsamarium intermediate **26**, resulting from α-cleavage of the ketyl radical **24** and subsequent reduction of radical **25** by a second molecule of SmI_2 (Scheme 6). The intermediate **26** can also be respon-

Scheme 6



sible for the formation of the alcohol **22**, through nucleophilic addition of oxygen. Diene **23** most probably arises by spontaneous dehydration of **22**.

The results obtained in studies with aldehydes **1** show that monophenyl or diphenyl substitution on the alkene moiety does not provide the stabilization required to promote the carbonyl-alkene reductive coupling process. As a result, alternative reaction pathways via ketyl radical intermediates, such as fragmentations and oxidations, are observed.

Although SmI_2 has been previously employed to mediate C−C bond fragmentations,[7] to the best of our knowledge, the reaction documented above represents the first example of a decarbonylation process taking place in β,γ-unsaturated aldehydes promoted by this reagent. It is noteworthy that this process, reminiscent of the well-known photochemical Norrish type I reaction, has also been observed when radical-anion intermediates of β,γ-unsaturated aldehydes are generated photochemically using SET-sensitizers.[1]

A study of the reactivity of the 4-cyanophenyl substituted aldehyde **27** and ketone **28** was carried out to determine if the presence of a cyano group attached to the phenyl ring would provide sufficient activation of the alkene unit to promote intramolecular reductive coupling. Treatment of **27** and **28** with SmI_2 promotes formation of the corresponding cyclopropanols **29** and **30** in 54% and 23% yield, respectively (Scheme 7). Therefore, conjugation of the alkene moiety with a 4-cyanophenyl group promotes the 3-*exo*-*trig* cyclization. The reaction of phenyl ketone **28** also affords the alcohol **31** (19%) resulting from reduction of the carbonyl group.

Interestingly, cyclopropanol **29** was isolated as a 1:1 mixture of *Z*/*E* diastereomers, whereas cyclization of phenyl ketone **29** yields the (*E*)-cyclopropanol **30** selectively. The reasons for the lack of diasteroselectivity observed in the reaction of aldehyde **27** are unclear at this point.

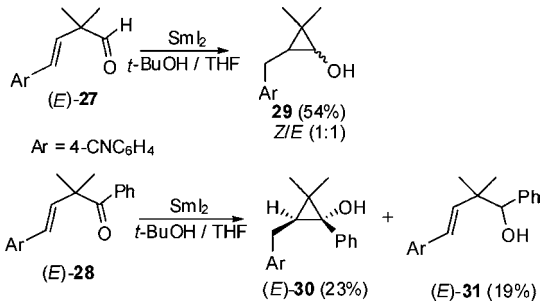
Finally, the reactivity of ketones **32** and **33**,[8] possessing two cyano groups directly bound to the alkene unit, was

(6) (a) Bezzenine-Lafollée, S.; Guibé, F.; Villar, H.; Zriba, R. *Tetrahedron* **2004**, *60*, 6931–6944. (b) Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Guillerez, M.-G. *Synlett* **2005**, 2362–2366. (c) Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Magnier-Boubier, C. *Tetrahedron Lett.* **2007**, *48*, 8234–8237.

(7) Williams, D. B. G.; Blann, K.; Caddy, J. *Org. Prep. Proc.* **2001**, *33*, 565–602.

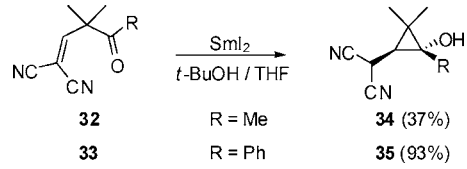
(8) Efforts made to synthesize the aldehyde analogue (4,4-dicyano-2,2-dimethyl-3-butenal) by deprotection of its corresponding acetal or thioacetal, as well as by reduction of methyl 4,4-dicyano-2,2-dimethylbut-3-enoate, failed.

Scheme 7. SmI_2-Mediated 3-*exo-trig* Cyclization of 4-Cyanophenyl-Substituted Compounds **27** and **28**



investigated. Reactions of **32** and **33** with SmI_2 yield the respective (*E*)-cyclopropanols **34** (37%) and **35** (93%) (Scheme 8).

Scheme 8. SmI_2-Mediated 3-*exo-trig* Cyclization of Dicyano-Substituted Ketones **32** and **33**



These results described above show that the 3-*exo-trig* cyclization of β,γ-unsaturated carbonyl compounds occurs not only with ester groups at the γ-position, as has been previously reported, but also with other electron-withdrawing substituents, such as cyano and 4-cyanophenyl groups.

In summary, the SmI_2-mediated 3-*exo-trig* cyclization of β,γ-unsaturated carbonyl compounds to produce cyclopropanols has been observed only infrequently.[6] The examples reported in the literature include compounds bearing an ester group attached to the alkene unit. However, the current effort demonstrates that this reaction can also take place when other electron-withdrawing groups, such as cyano and 4-cyanophenyl, are present, affording the corresponding cyclopropanols in good to excellent yields. Interestingly, aromatic moieties, such as fluororene and indene, also promote the cyclization process, probably owing to the enhanced stability of the cyclopropyl intermediates. In contrast, monophenyl or diphenyl substitution do not provide the necessary stabilization required for the cyclization to occur, thus opening new reaction pathways for the ketyl radical intermediates, such as fragmentations to yield alkenes, and oxidation.

The results outlined above increase considerably the synthetic potential of the 3-*exo-trig* cyclizations of β,γ-unsaturated carbonyl compounds, a method that enables the synthesis of differently functionalized cyclopropanols that can be present in a wide range of natural products and synthetic building blocks.[9]

Acknowledgment. We thank the Spanish Ministerio de Ciencia e Innovación (MICINN, CTQ2008-02820) and the Universidad Complutense de Madrid (Grant No. GR58/08) for financial support. We acknowledge the support provided by the Centro de Resonancia Magnetica Nuclear and the Centro de Microanálisis of the Universidad Complutense de Madrid.

Supporting Information Available: Experimental procedures for the preparation of β,γ-unsaturated carbonyl compounds **8**, **9**, **27**, **28**, and **33** and general procedure for the reactions with SmI_2. Analytical and spectroscopic data and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101666M

(9) Kulinkovich, O. G. *Chem. Rev.* **2003**, *74*, 2597–2632.