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Medium-Sized Carbocycles by Samarium Diiodide-Induced Carbonyl−Alkene Cyclizations

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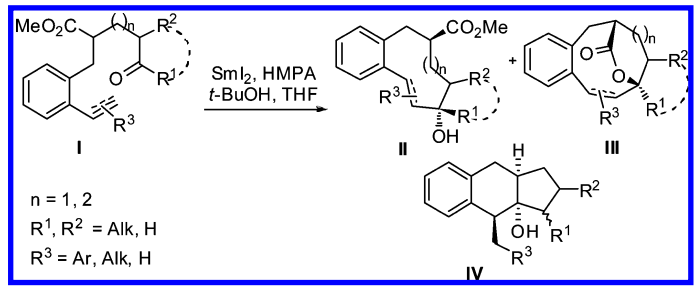
ABSTRACT



Intramolecular samarium diiodide-induced carbonyl−alkene or carbonyl−alkyne coupling reactions afforded without high dilution conditions 9- and 10-membered benzannulated carbocycles of type II and III in surprisingly good yields and stereoselectivities. A novel samarium diiodide-mediated cascade process leading to tricyclic compounds of type IV was also observed. Bisbenzannulated 10- and 11-membered carbocycles were prepared in very good yields.

Samarium diiodide was introduced as a reagent for organic synthesis by Kagan and his co-workers.[1] Over the years this selective electron transfer agent has gained remarkable importance due to its unique properties. It promotes a variety of synthetic transformations, providing products often with high regio- and stereoselectivity and under mild reaction conditions.[2] One of the areas where SmI_2 may be applied is the construction of medium-sized rings, which are key structural features of a wide range of biologically active compounds or natural products.[3] SmI_2 has been reported to successfully facilitate formation of medium-sized carbocycles in a number of ways. For example, 8-, 9-, 11-membered and even larger rings were synthesized by intramolecular Reformatsky-type reactions of α-bromoesters with aldehydes.[4a] The related Barbier couplings of allyl chlorides with aldehydes[4b] and ketones[4c] furnished 8- and 9-membered carbocycles. Molander et al. constructed cyclooctanol derivatives by radical couplings of ketones with alkenes.[4d] Indirect methods used SmI_2 in sequential reactions, generating intermediates which either form the desired carbocycles via

† Responsible for X-ray analyses.

(1) Namy, J. L.; Girard, P.; Kagan, H. B. *New J. Chem.* **1977**, *1*, 5–7.

(2) Reviews: (a) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607–637. (b) Ebran, J.-P.; Jensen, C. M.; Johannesen, S. A.; Karaffa, J.; Lindsay, K. B.; Taaning, R.; Skrydstrup, T. *Org. Biomol. Chem.* **2006**, *4*, 3553–3564. (c) Concellon, J. M.; Rodriguez-Solla, H. *Eur. J. Org. Chem.* **2006**, *161*, 3–1625. (d) Jung, D. Y.; Kim, Y. H. *Synlett* **2005**, 3019–3032. (e) Edmonds, D. J.; Johnston, D.; Procter, D.-J. *Chem. Rev.* **2004**, *104*, 3371–3404. (f) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422–438. (g) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (h) Steel, P. G. *J. Chem. Soc., Perkin Trans. I* **2001**, 2727–2751. (i) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777. (j) Kagan, H. B.; Namy, J. L. *Top. Organomet. Chem.* **1999**, *2*, 155–198. (k) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354. (l) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338.

(3) Selected reviews: (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239–273. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930. (c) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757–5821.

(4) (a) Inanaga, J.; Yokoyama, Y.; Hanada, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1991**, *32*, 6371–6374. (b) Matsuda, F.; Sakai, T.; Okada, N.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 863–864. (c) Tamiya, H.; Goto, K.; Matsuda, F. *Org. Lett.* **2004**, *6*, 545–547. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186–3192.

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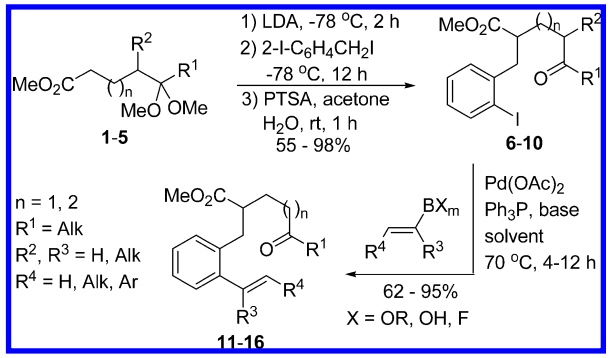
intramolecular SmI_2-induced acyl substitutions[5a−d] to give 7- to 9-membered rings or by fragmentation reactions leading to 8- to 10-membered carbocycles.[5e]

Our group has utilized SmI_2 for cyclizations of a variety of ketones bearing γ-(2-alkenyl)aryl or γ-(2-alkynyl)aryl moieties which furnished benzannulated cycloheptanol,[6c] cyclooctanol[6a−c,2f] and cyclooctenol[6d,2f] derivatives. In continuation of this work we have now extended our method to the synthesis of larger rings. Herein we describe an approach to 9-, 10-, and 11-membered carbocycles via SmI_2-induced ketyl−alkene and ketyl−alkyne cyclization reactions.

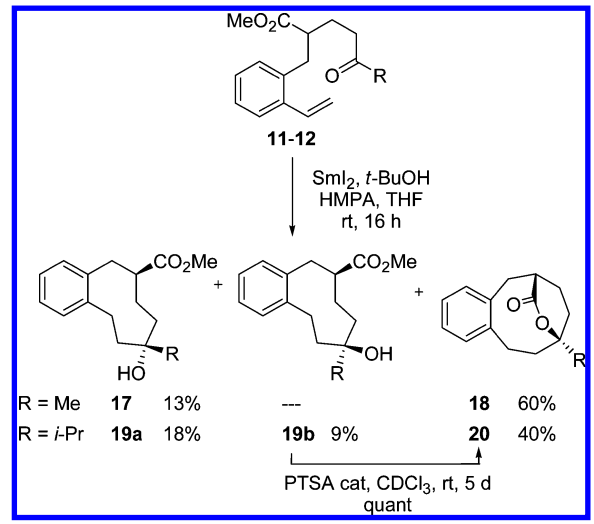
The preparation of starting materials was easy starting from protected δ- and ε-ketoesters **1**−**5** which are available by standard methods. Alkylation of compounds **1**−**5** with 2-iodobenzyl iodide followed by ketal cleavage under acidic conditions furnished key intermediates **6**−**10** (Scheme 1). These were then equipped with different alkenyl groups by using Suzuki-coupling reactions[7a−d] to furnish cyclization precursors **11**−**16**.

Scheme 1. Synthesis of Alkenyl-Substituted δ- and ε-Ketoesters **11**−**16**



To our delight compound **11**, the simplest precursor of 9-membered ring analogous to our previously described systems, reacted with SmI_2 under standard conditions (2.2 equiv of SmI_2, 18 equiv of HMPA,[8] 2.0 equiv of *t*-BuOH in THF) to furnish a 1:4.6 mixture of benzannulated cyclononane derivatives **17** and **18** in 73% combined yield. The intermediate with cis-arrangement of the methoxycarbonyl group and the samariumoxy moiety is favored, which leads to the formation of the γ-lactone bridge of **18** (Scheme 2). The analogous 8-membered product was isolated in only 41% yield, giving the trans-isomer predominantly (3.1:1).[6b] A bulkier substituent adjacent to the carbonyl group was well tolerated as demonstrated by the isopropyl-substituted compound **12**, which furnished cyclization products **19/20** in 67% combined yield. Again a clear preference for the lactone-bridged products **20** and its cis-configured precursor **19b** was observed over trans-compound **19a** (Scheme 2). The δ-hydroxyester **19b** was converted into **20** under acid catalysis. Remarkably, the analogous 8-membered product was formed in 84% yield with exclusive trans selectivity.[6b]

Scheme 2. Samarium Diiodide-Induced 9-*endo-trig* Cyclizations of Styryl-Substituted δ-Ketoesters **11** and **12**



Models explaining the observed stereoselectivities are so far speculative. A transition state as presented in Figure 1 for the 9-*endo-trig* cyclization of styryl-substituted δ-ketoesters such as **11** and **12** can rationalize the preferred formation of cis-products. As a crucial feature we position the methoxycarbonyl and the R substituents in extra-annular positions. The samarium ketyl approaches the alkene in an antiperiplanar fashion hence leading to a staggered conformation. As a result cis-products are obtained in preference. Certainly, more detailed studies are required to substantiate these ideas.

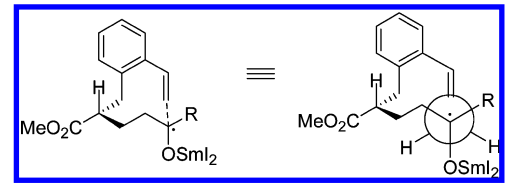


Figure 1. Suggested transition state for 9-*endo-trig* cyclizations of styryl-substituted δ-ketoesters such as **11** or **12** leading to cis-products (HMPA ligands at samarium are omitted for simplicity).

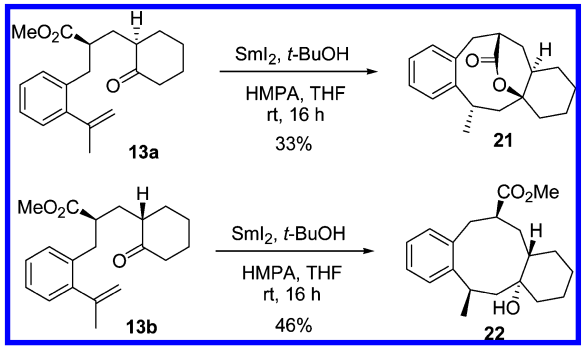
(5) (a) Molander, G. A.; Alonso-Alija, C. *J. Org. Chem.* **1998**, *63*, 4366–4373. (b) Molander, G. A.; Machrouhi, F. *J. Org. Chem.* **1999**, *64*, 4119–4123. (c) Molander, G. A.; Koellner, C. *J. Org. Chem.* **2000**, *65*, 8333–8339. (d) Molander, G. A.; Brown, G. A.; Storch de Gracia, I. *J. Org. Chem.* **2002**, *67*, 3459–3463. (e) Molander, G. A.; Le Huerou, Y.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511–4516.

(6) (a) Khan, F. A.; Czerwonka, R.; Zimmer, R.; Reissig, H.-U. *Synlett* **1997**, 995–997. (b) Reissig, H.-U.; Khan, F. A.; Czerwonka, R.; Dinesh, C. U.; Shaikh, A. L.; Zimmer, R. *Eur. J. Org. Chem.* **2006**, 4419–4428. (c) Saadi, J.; Reissig, H.-U. *Synlett* **2009**, in press. (d) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267–4277.

(7) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (b) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107–109. (c) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424–8429. (d) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (f) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

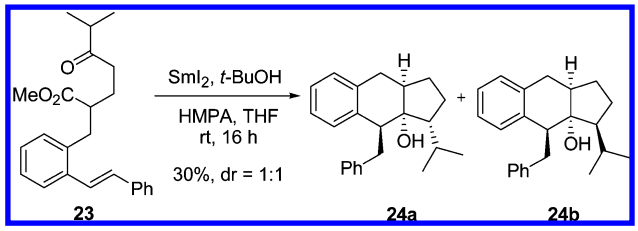
SmI_2-induced reactions of the two diastereomeric cyclic δ-ketoesters **13a** and **13b** (Scheme 3) demonstrate that higher substituted precursors also undergo 9-*endo-trig* cyclizations affording fairly complex cyclononane derivatives **21** and **22** in low or moderate yields but with excellent stereoselectivities.[9] Remarkably, the methyl group at the newly formed stereogenic center was found to be in a trans relationship to the hydroxyl group (similar to that in analogous cyclooctanol derivatives[6c]).

Scheme 3. Samarium Diiodide-Induced 9-*endo-trig* Cyclizations of Isopropenyl-Substituted Cyclic δ-Ketoesters **13a** and **13b**



Stilbenyl-substituted δ-ketoester **23** was prepared by a Heck reaction[7e] of **7** with styrene. To our surprise, its cyclization gave two diastereomers (dr = 1:1) of the unexpected tricyclic product **24** in 30% yield together with 29% of starting material (Scheme 4). The structure and

Scheme 4. Samarium Diiodide-Induced Cascade Reaction of Stilbenyl-Substituted δ-Ketoester **23**



relative configuration of **24a** was unambiguously determined by X-ray crystallography (Figure 2). We assume that these products result from a SmI_2-induced 5-*exo-trig* ketyl−methoxycarbonyl coupling,[10a] followed by a SmI_2-mediated α-hydroxyketone deoxygenation[10b] and a SmI_2-induced 6-*exo-trig* ketyl−alkene coupling.[10c] Remarkably, this experiment was performed with only 2.4 equiv of SmI_2. The sequence most probably requires 6 equiv of SmI_2 for completion.[11] To the best of our knowledge the transformation **23** to **24** is the first one with these steps occurring in a sequential manner.

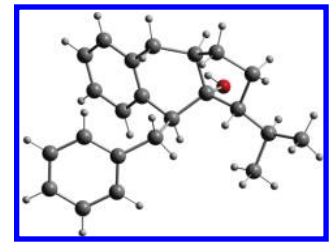
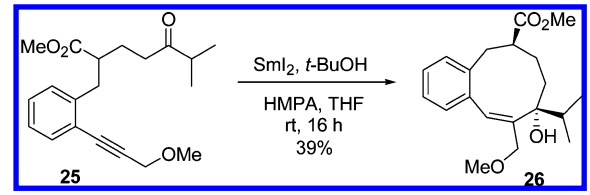


Figure 2. Molecular structure (Diamond[12]) of tricyclic compound **24a**.

For the investigation of related alkynyl-substituted compounds we prepared δ-ketoester **25** by Sonogashira coupling[7f] of **7** with 3-methoxyprop-1-yne. Its SmI_2-promoted 9-*endo-dig* cyclization furnished cyclononenol derivative **26** in moderate yield (Scheme 5).[6d,13] This protocol gives access to medium-sized rings featuring an attractive allylic alcohol function opening many possibilities for their further functionalization.[14]

Scheme 5. Samarium Diiodide-Induced 9-*endo-dig* Cyclization of 3-Methoxypropynyl-Substituted δ-Ketoester **25**



Encouraged by these results we examined SmI_2-promoted cyclizations for the construction of larger rings. Upon exposure to SmI_2 the methyl ketone **14** provided the desired cyclodecanol **27** in 54% yield as a 2:1 mixture of two diastereomers (Scheme 6). Increase of the size of the substituent adjacent to the carbonyl group retarded the cyclization. The isopropyl-substituted ε-ketoester **15** furnished product **28** in only 26% yield as an inseparable 1.4:1

(8) For the role of HMPA see: (a) Flowers, R. A., II *Synlett* **2008**, 1427–1439. (b) Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2008**, *130*, 7228–7229. (c) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 865–867. (d) Inokuchi, T. *J. Org. Chem.* **2005**, *70*, 1497–1500. (e) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers, R. A., II *J. Am. Chem. Soc.* **2000**, *122*, 7718–7722. (f) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317–318.

(9) Many cyclizations with SmI_2 provide only moderate or low yields. In general, no additional products could be isolated. In several cases fragmentation products could be identified. For examples see ref 6b.

(10) (a) Liu, Y.; Zhang, Y. *Tetrahedron Lett.* **2001**, *42*, 5745–5748. (b) Kamochi, Y.; Kudo, T.; Masuda, T.; Takadate, A. *Chem. Pharm. Bull.* **2005**, *53*, 1017–1020. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132–3139.

(11) A suggestion for the detailed mechanism is presented in the Supporting Information.

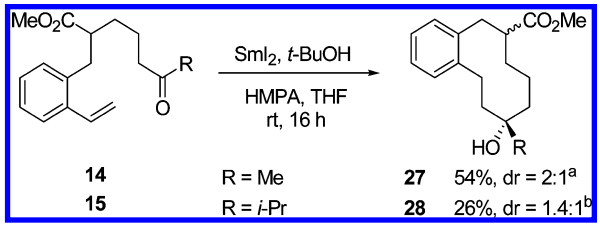
(12) Crystal Impact GbR Diamond software ver. 2.1d.

(13) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236–8246.

(14) E.g.: (a) Dudley, G. B.; Danishefsky, S. J *Org. Lett.* **2001**, *3*, 2399–2402. (b) Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 2732–2735.

mixture of diastereomers. These results indicate a higher sensitivity of the 10-*endo-trig* process to steric hindrance. It

Scheme 6. Samarium Diiodide-Induced 10-*endo-trig* Cyclizations of Styryl-Substituted ε-Ketoesters **14** and **15**[b]

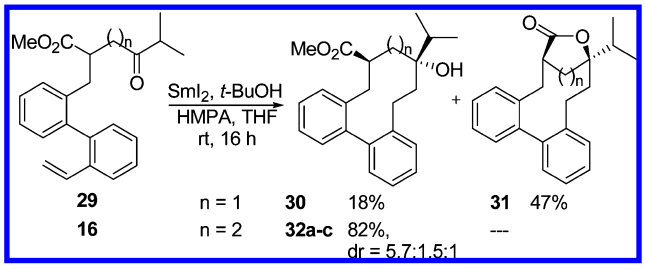


[a] As separable diastereomers. [b] As inseparable mixture; dr determined by the integration of NMR signals of the methoxy groups.

is also reasonable that in both reactions no lactone bridge was formed since ε-lactones are kinetically and thermodynamically much less preferred. The flexibility of the cyclodecane ring and the distance between the two stereocenters so far did not allow assignment of the relative configuration of these compounds by NMR spectroscopy.

The efficacy of the 10-*endo-trig* cyclization was strongly improved by use of ketoesters bearing 2′-vinylbiphenyl moieties.[15] Starting material **29** was prepared (analogously to **16**) from the corresponding 2-iodobenzyl-substituted γ-ketoester[6b] by Suzuki-coupling with commercially available 2-vinylphenylboronic acid. It afforded bisbenzannulated cyclodecanol derivatives **30** and **31** in 65% combined yield and with a stereoselectivity of 2.6:1 in favor of the lactone-bridged cis-product **31** (Scheme 7). The higher homologue-

Scheme 7. Samarium Diiodide-Induced 10- and 11-*endo-trig* Cyclizations of the 2′-Vinylbiphenyl-Substituted γ- and δ-Ketoesters **29** and **16**



δ-ketoester **16** underwent the 11-*endo-trig* cyclization with excellent efficacy affording three diastereoisomeric products **32a**−**c** in 82% combined yield and in 5.7:1.5:1 ratio. The relative configuration of the major stereoisomer **32a** was unambiguously determined by X-ray crystallography (Figure 3). The configurations of the two minor diastereomers could not be assigned so far, but we assume that one should also be a trans-product, however, with an alternate orientation of the chiral axis with respect to the stereogenic centers.

The X-ray structure determination of the major undecanol derivative **32a** shows that the dihedral angle between both aromatic rings is 67.0(1)° (Figure 3). The bond linking the two aryl rings is slightly bent (intersection angle of the lines C8, C11 and C12, C15 4.9°) by the strain of the 11-membered ring.

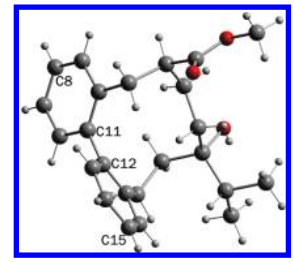


Figure 3. Molecular structure (Diamond[12]) of the major undecanol derivative **32a**.

In conclusion, we have demonstrated that SmI_2-induced radical cyclizations are a surprisingly efficient tool for the construction of medium-sized benzannulated carbocycles. Several 9-, 10-, and 11-membered rings have been synthesized in moderate to good yields and with good stereoselectivities. This method is especially attractive as it is functional-group compatible, and starting materials are readily available from simple and inexpensive building blocks, allowing a wide range of variations. Further investigations are required to explore the scope and limitations of this method and factors determining the stereoselectivity.

Acknowledgment. Generous support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Bayer Schering Pharma AG is most gratefully acknowledged. We thank R. Zimmer for help during preparation of this manuscript.

Supporting Information Available: Experimental procedures, detailed mechanistic suggestions for the described cascade reaction leading to compounds **24**, X-ray crystallographic data, and complete characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For an example of a carbonyl−alkene coupling with a biphenyl moiety leading to a dibenzocyclooctadiene system see: Molander, G. A.; George, K. M.; Monovich, L. G. *J. Org. Chem.* **2003**, *68*, 9533–9540.