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Stereoselective Formation of Tri- and Tetracycles by Samarium Diiodide-Induced Cyclizations of Naphthyl-Substituted Ketones

Mathias Berndt, Iva Hlobilová, and Hans-Ulrich Reissig*

Institut für Chemie, Freie Universität Berlin, Takustr. 3, D-14195 Berlin, Germany

hans.reissig@chemie.fu-berlin.de

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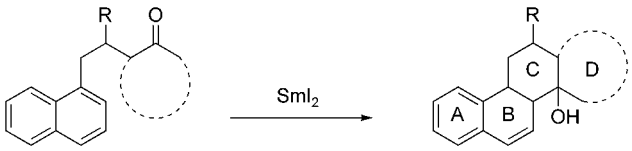
ABSTRACT



Samarium diiodide promotes smooth reductive cyclizations of γ-naphthyl-substituted ketones to afford tri- and tetracyclic compounds in high yields and with excellent stereoselectivities. Cyclic ketones furnish steroid-like compounds with "unnatural" cis/cis annulation of rings B/C/D. The remaining styrene-type double bond of ring B allows further stereoselective reactions. Cases with matched and mismatched relative configuration could be identified leading to dramatic differences in the ring closure ability.

Since the pioneering work of Kagan,[1] samarium diiodide has become a powerful and versatile reagent in organic synthesis.[2] One important application of this one-electron-transfer reagent is the intramolecular coupling of carbonyl groups with carbon−carbon multiple bonds, which generally leads to highly functionalized products with excellent diastereoselectivities. In particular, ketyl olefin couplings have been examined by Molander et al. in very much detail.[3]

We recently demonstrated that cyclizations of samarium ketyls with alkynyl,[4] aryl,[5] or hetaryl substituents[6] lead to interestingly functionalized compounds such as cyclooctenols **2**, hexahydronaphthalenes **4**, or indole derivatives **6** (Scheme 1). The intramolecular cyclizations of γ-aryl ketones **3** occur with dearomatization of the arene moiety generating a synthetically useful 1,4-cyclohexadienyl subunit.[5] Starting from related aniline derivatives, the corresponding quinolines are smoothly accessible.[6] These reactions are induced by the samarium diiodide−HMPA complex,[7] which transfers an electron to the carbonyl group, generating a radical anion.

(1) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693−2698.

(2) Selected reviews on samarium diiodide-mediated reactions: (a) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573−6614. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. (c) Khan, F. A.; Zimmer, R. *J. Prakt. Chem.* **1997**, *339*, 101−104. (d) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321−3354. (e) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745−777. (f) Kagan, H. B.; Namy, J. L. *Top. Organomet. Chem.* **1999**, *2*, 155−198. (g) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727−2751. (h) Hölemann, A. *Synlett* **2001**, 1497−1498. (i) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372. (j) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, in press.

(3) (a) Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236−8246. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132−3139. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1994**, *59*, 3186−3192. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872−882.

(4) (a) Nandanan, E.; Dinesh, C. U.; Reissig, H.-U. *Tetrahedron* **2000**, *56*, 4267−4277. (b) Hölemann, A. Ph.D. *Dissertation* **2004**, Freie Universität Berlin.

(5) (a) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem.* **1999**, *111*, 874−876; *Angew. Chem., Int. Ed.* **1999**, *38*, 789−791. (b) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290−1292. Related examples: (c) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem.* **1995**, *107*, 2597−2599; *Angew. Chem. Int. Ed.* **1995**, *34*, 2383−2385. (d) Kuo, C.-W.; Fang, J. M. *Synth. Commun.* **2001**, *31*, 877−892. (e) Ohno, H.; Wakayama, R.; Maeda, S.; Iwasaki, H.; Okumura, M.; Iwata, C.; Mikamiyama, H.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5909−5916. (f) Ohno, H.; Okumura, M.; Maeda, S.; Iwasaki, H.; Wakayama, R.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 7722−7732.

(6) (a) Gross, S.; Reissig, H.-U. *Synlett* **2002**, 2027−2030. (b) Gross, S.; Reissig, H.-U. *Org. Lett.* **2003**, *5*, 4305−4307.

(7) HMPA strongly raises the reducing power of samarium diiodide and is required for most ketyl coupling reactions. See: (a) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485−1486. (b) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6895−6899.

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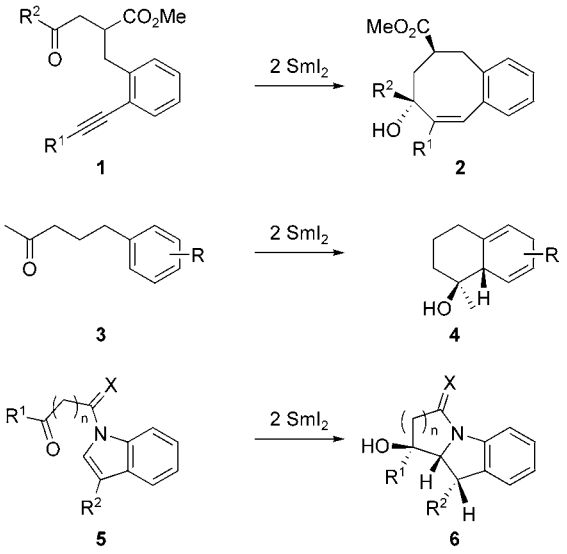
Scheme 1



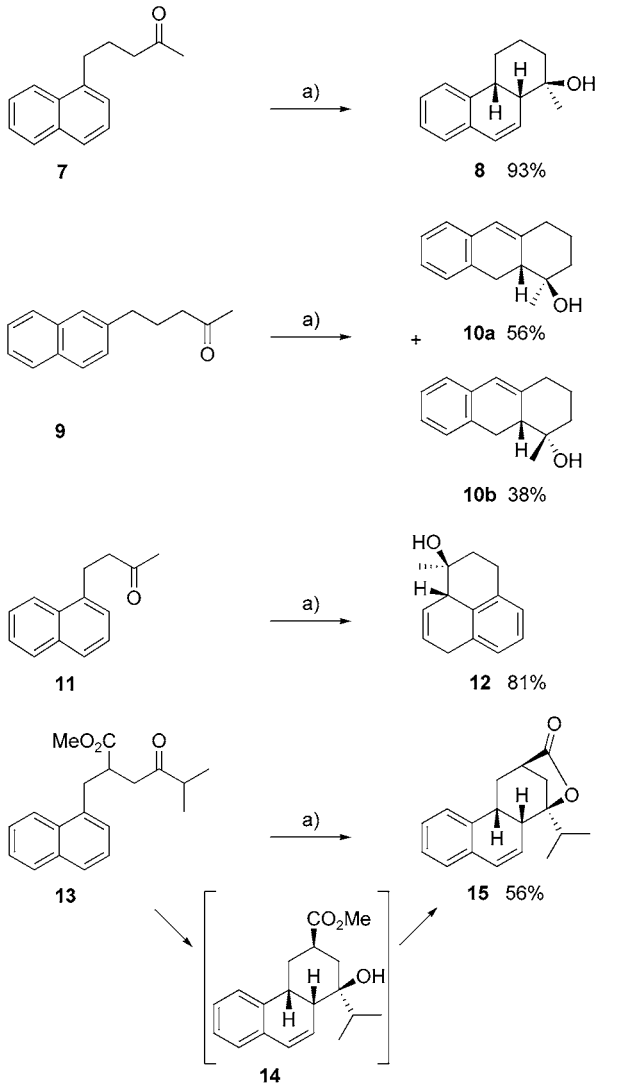
This samarium ketyl attacks the ortho position of the arene ring and forms the new six-membered ring. A second electron transfer and regioselective protonation provide the bicyclic products.

Here we present the application of this coupling method to naphthalene units as samarium ketyl acceptors, which should lead to highly functionalized tri- and tetracyclic compounds.

We started our investigations with easily accessible[8] naphthyl-substituted methyl ketones **7**, **9**, and **11** (Scheme 2), which afforded tricyclic products **8**, **10**, and **12** in superb yields. While tricycle **8** was formed as a single stereoisomer, compound **10** was produced as a 60:40 mixture of two diastereomers.[9] Remarkably, β-naphthyl ketone **11**[10] furnished only compound **12** with formation of a new six-membered ring and not the conceivable regioisomer containing a five-membered ring[11] (Scheme 2).

The protonation of the anionic intermediates proceeds highly regioselectively. Whereas styrene-like substructures were generated in **8** and **10**, an unconjugated double bond

Scheme 2 [a]



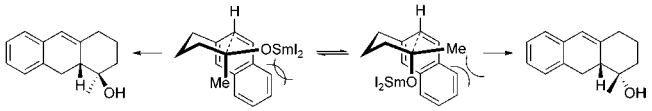
[a] Conditions: 2.2 equiv of SmI_2, THF, 18 equiv of HMPA, 2.0 equiv of *t*-BuOH, rt.

resulted for **12**. In all cases, one aromatic ring is conserved. The change from a phenyl to a naphthyl unit as samarium ketyl acceptor resulted in a considerable increase in reactivity. While transformations of phenyl-substituted substrates occur with complete loss of aromaticity, this is only partially abrogated in the case of naphthyl-substituted ketones.

The superior driving force of reductive cyclizations of naphthyl-substituted ketones was clearly indicated by the conversion of precursor **13**[12] bearing an *i*-propyl ketone unit. While the analogous phenyl-substituted substrates completely failed to undergo the samarium diiodide-induced cyclizations,[13] reaction of **13** afforded tetracyclic lactone **15**.

(8) Compounds **7** and **9** were synthesized by Heck reaction of the corresponding bromonaphthalenes and 4-pentene-2-ol according to a known procedure: Taylor, E. C.; Wang, Y. *Heterocycles* **1998**, *48*, 1537−1553.

(9) An explanation for the lack of diastereoselectivity in the formation of **10** may be the steric interaction of the very bulky $OSmI_2$ substituent and the naphthalene ring in the transition structure. Generally, this group seems to prefer equatorial positions, when arene rings are the acceptor, however, the spatially extended naphthalene ring apparently changes this situation:



(10) Ketone **11** was synthesized by alkylation of methyl 3-oxobutanoate with 1-bromomethylnaphthalene, followed by saponification and decarboxylation. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082−1087. Autorenkollektiv. *Organikum*, 18th ed.; Deutscher Verlag der Wissenschaften: Berlin, 1990; p 519.

(11) Compound **12** was already synthesized by cathodic reduction of the corresponding ketone **11**: Kise, N.; Suzumoto, T.; Shono, T. *J. Org. Chem.* **1994**, *59*, 1407−1413.

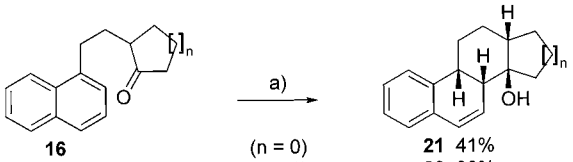
(12) Precursor **13** was prepared by the highly flexible sequence via siloxycyclopropanecarboxylates as published earlier; the alkylating agent in this case was 1-bromomethylnaphthalene: (a) Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 531−551. (b) Kunkel, E.; Reichelt, I.; Reissig, H.-U. *Liebigs Ann. Chem.* **1984**, 802−819. (c) Khan, F. A.; Czerwonka, R.; H.-U. Reissig, *Eur. J. Org. Chem.* **2000**, 3607−3617.

(13) Berndt, M. Ph.D. Dissertation, Freie Universität Berlin, Berlin, 2003.

Apparently, the intermediate tricyclic hydroxyl ester **14** cyclized to the γ-lactone under the applied reaction conditions.[14] The constitution and configuration of product **15** were unequivocally established by X-ray analysis.[15]

Employment of cyclic ketones as ketyl precursors instead of methyl ketones leads to products with steroid-like skeletons (Scheme 3). Naphthylethyl-substituted cycloalkanones **16**−**20**[16] were converted in moderate to very good yields into tetracyclic products **21**−**25** containing the corresponding four-, five-, six-, seven-, or eight-membered "D-ring". The diastereoselectivities are excellent, providing compounds bearing all bridgehead substituents at the same face, which leads to a bowl-like shape of these molecules. This synthetic method thus allows easy access to steroid mimics with entirely "unnatural" configuration.

Scheme 3 [a]

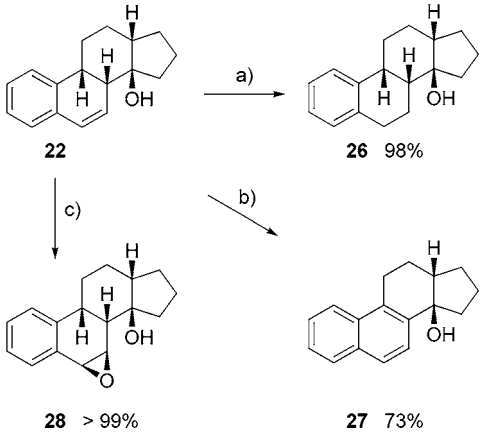


[a] Conditions: 2.2 equiv of SmI_2, THF, 18 equiv of HMPA, 2.0 equiv of *t*-BuOH, rt.

The styrene-type double bond of products **21**−**25** allows a variety of synthetic modifications, and first examples with **22** as the precursor are depicted in Scheme 4. Reduction by catalytic hydrogenation or oxidation with MnO_2[17] led to expected products **26** and **27**. Reaction of **22** with *m*-chloroperbenzoic acid quantitatively afforded epoxide **28**, where the introduction of the oxygen had occurred stereoselectively from the less hindered convex face of the molecule and cis to the bridgehead hydroxyl group. An X-ray analysis of **28** provided conclusive evidence for its configuration and that of precursor **22**.[18]

The relative configurations of starting materials have a crucial influence on the efficiency of the ketyl arene couplings, and we identified "matched" and "mismatched" cases. Methoxycarbonyl-substituted cyclopentanone derivative **29**[19] gave the expected tetracyclic product **30** almost

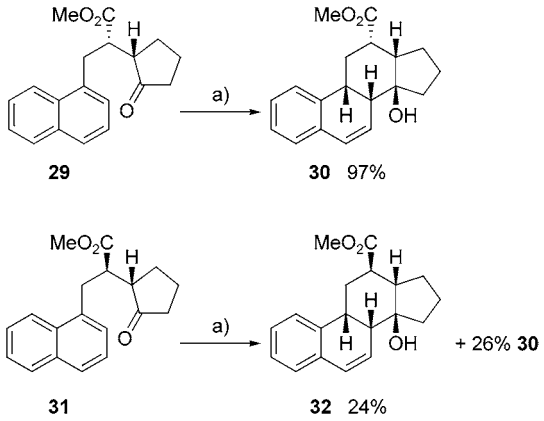
Scheme 4 [a]



[a] Conditions: (a) Pd/C, H_2, MeOH, rt; (b) MnO_2, THF, D; (c) *m*-CPBA, MeOH, 0 °C.

quantitatively and as a single isomer (Scheme 5), whereas its diastereoisomer **31** led to a mixture of the expected **32** and **30** in moderate yield. Apparently, precursor **31** is the "mismatching" isomer for the reductive cyclization and thus leads to slow formation of **32**, which is accompanied by partial epimerization of **31** to **29** and hence formation of the "wrong" diastereomer **30**.

Scheme 5 [a]



[a] Conditions: 2.2 equiv of SmI_2, THF, 18 equiv of HMPA, 2.0 equiv of *t*-BuOH, rt.

Interestingly, the ring size of the cycloalkanone units seems to have great influence on the preferred transition structures during cyclization. The methoxycarbonyl-substituted cyclohexanones showed opposing match and mismatch. Substrates **33** and **36** afforded the expected tetracycles **34** and **37** together with lactones **35** and **38**, both probably derived from the corresponding primary cyclization products (Scheme 6).[20]

(14) Similar lactonizations of related γ-hydroxy carboxylic esters are known: Khan, F. A.; Czerwonka, R.; Zimmer, R.; Reissig, H.-U. *Synlett* **1997**, 995−997. See also ref 4a.

(15) Berndt, M.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Z. Kristallogr. NCS* **2004**, submitted.

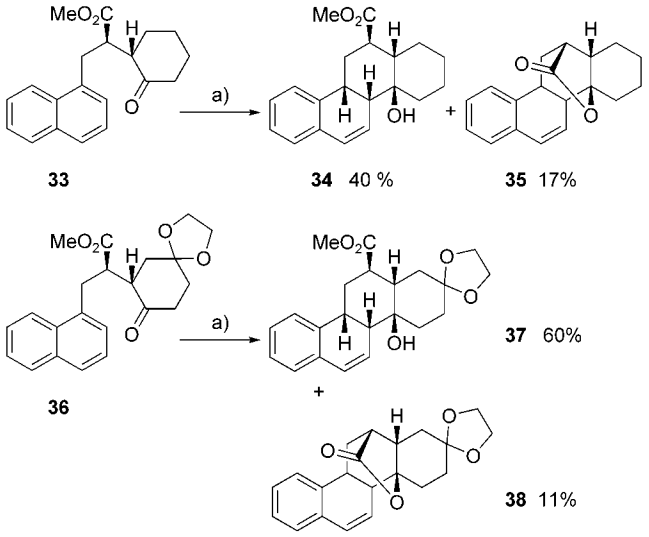
(16) Compounds **16**−**20** were obtained by LDA-promoted alkylation of *N*-cyclohexyl imines of the corresponding cycloalkanones with 1-(2-iodoethyl)naphthalene as an electrophile. For analogous procedures, see: (a) Fleming, I.; Godhill, J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1493−1498. (b) Fleming, I.; Godhill, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1563−1570. (c) Wallace, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3169−3171.

(17) Bonnaud, B.; Bigg, D. C. H. *Synthesis* **1994**, 465−467.

(18) Berndt, M.; Brüdgam, I.; Hartl, H.; Reissig, H.-U. *Z. Kristallogr. NCS* **2004**, submitted.

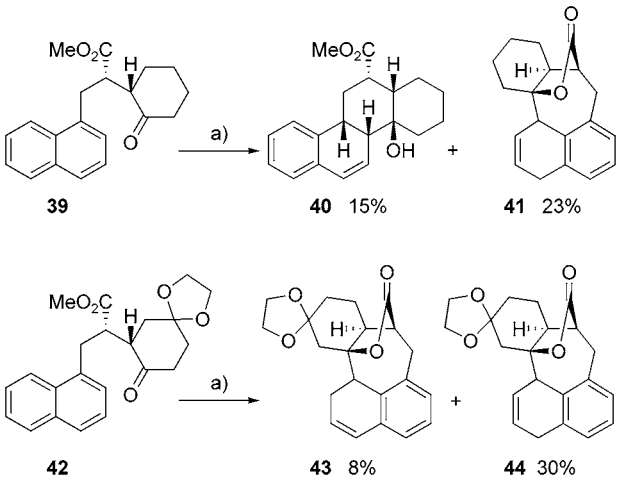
(19) **29**, **31**, **33**, and **39** were synthesized starting from cyclopentanone or cyclohexanone as described in ref 12. Diastereomers **36** and **42** were prepared similarly with the corresponding ketal as a starting material.

Scheme 6 [a]



[a] Conditions: 2.2 equiv of SmI_2, THF, 18 equiv of HMPA, 2.0 equiv of *t*-BuOH, rt.

Scheme 7 [a]



[a] Conditions: 2.2 equiv of SmI_2, THF, 18 equiv of HMPA, 2.0 equiv of *t*-BuOH, rt.

The reactions of the diastereomeric ketones **39** and **42** led to polycyclic frameworks such as **41**, **43**, and **44** (Scheme 7), which are formed by attack of the ketyl to the 8-position of the naphthalene ring and not to the 2-position. New seven-membered rings were formed followed by lactonization. Starting from **39**, the expected product **40** containing a six-membered ring was isolated in only 15% yield together with 9% of another benzophenanthrene-type product of yet unknown configuration. The influence of the ring size of the cycloalkanone unit on these cyclizations is not yet understood and still under investigation.[21]

We demonstrated that γ-naphthyl-substituted ketones are generally excellent substrates for samarium diiodide-promoted cyclizations resulting in tricyclic and tetracyclic products in high yields and diastereoselectivity. The tetracycles resemble steroids, although their configuration is entirely "unnatural". The corresponding derivatives bearing additional oxygen functionalities in rings A and D of these compounds will be prepared to study the biological activity of the resulting steroid mimics. The cyclization behavior of substrates with two given stereogenic centers needs further clarification to understand fully the stereochemical features of these reactions.

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Supporting Information Available: Detailed description of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Configurations of compounds **35**, **38**, **41**, **43**, and **44** have so far not been fully established due to extended overlap of the ^{1}H NMR signals.

(21) Chair-like folding in the transition structure of **33** or **36** with the methoxycarbonyl group in an equatorial position would lead to compounds as depicted in Scheme 6; on the other hand, no comparable chair folding seems to operate for the reactions presented in Scheme 5.