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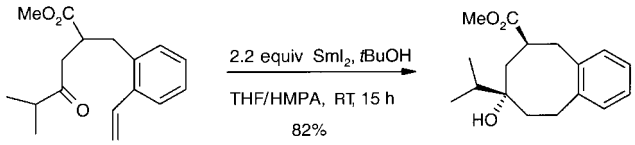
A New Samarium Diiodide Induced Reaction: Intramolecular Attack of Ketyl Radical Anions on Aryl Substituents with Formation of 1,4-Cyclohexadiene Derivatives**

Chimmanamada U. Dinesh and Hans-Ulrich Reissig*

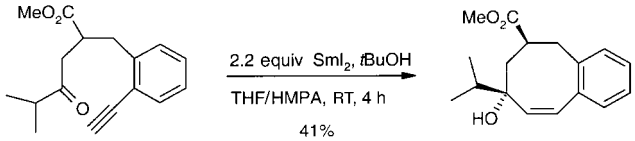
Dedicated to Professor Edward Piers on the occasion of his 60th birthday

Samarium diiodide was introduced by Kagan et al.[1] as a selective one electron transfer reagent in organic chemistry. Several variants of SmI_2-induced cyclization reactions[2] have attained synthetic importance owing to their high stereoselectivity and ability to undergo sequential reactions.[3] Frequently, ketyl radical anions generated by the electron transfer are the reactive species which add to a multiple bond offered at an appropriate distance. We now report that these ketyl radical anions can attack an aryl moiety in an intramolecular fashion and, after a second electron transfer, lead to 1,4-cyclohexadiene derivatives. This reaction has not yet been observed in samarium chemistry to the best of our knowledge, and it should gain considerable synthetic importance owing to its high diastereoselectivity.

Motivated by the examples reported by Molander and McKie,[4] we recently developed a synthesis of benzannulated cyclooctane derivatives.[5] Our previously unpublished example **1**→**2** (HMPA = hexamethyl phosphoramide) demonstrates that this samarium diiodide promoted transformation proceeds with high diastereoselectivity and in very good yield in spite of the sterically demanding isopropyl group. To explore further mechanistic details of the 8-*endo* cyclization and to obtain new options for functionalizations of the newly generated eight-membered ring, alkyne derivatives such as **3** were subjected to the general reaction conditions. The expected benzannulated cyclooctene **4** was isolated in 41% yield as a single diastereomer. To our knowledge this is the first successful 8-*endo-dig* cyclization of a samarium ketyl.[6]



1 **2**



3 **4**

Since they were more readily accessible,[7] the disubstituted alkynes **5**–**7** were first subjected to samarium diiodide cyclization conditions. However, we obtained products derived from neither an 8-*endo-dig* cyclization nor from the more likely 7-*exo-dig*-reaction, but surprisingly cyclohexadienes **11**–**13** which were formed by attack on aryl substituents. Examples **8** and **9** demonstrate that the alkyne units are not required for the cyclization, as samarium diiodide now affords cyclization products **14** and **15** or the lactone **16**. The cyclohexanone moiety in **6**–**8** allows smooth cyclization;[8] however, the steric hindrance in isopropyl derivative **10** seems to be too high. Under the conditions applied mainly starting material was recovered and no product was formed. The fact that **1** and **3** were transformed into bicyclic **2** and **4**, and that the precursor **10** was essentially inert, supports the reversibility of the first electron transfer to the carbonyl group. The subsequent steps are responsible for the productivity of the sequence.

Particularly remarkable is the high diastereoselectivity of the reaction, since in all examples only one diastereomer could be detected. The relative configuration at the two newly generated asymmetric centers of **14** was proven by X-ray analysis.[9] This showed not only the *cis* arrangement of the bridgehead hydrogen atom with respect to the hydroxyl group, but also the location of R^2 and of the methoxycarbonyl

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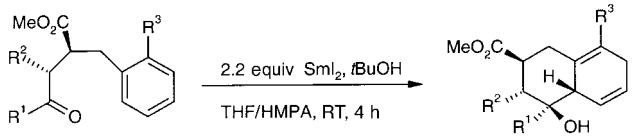


5 - 10 **11 - 15**

5, R^1 = Me, R^2 = H, R^3 = $-C\equiv C-SiMe_3$ **11**, 50%

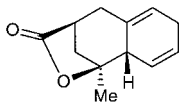
6, R^1,R^2 = $-(CH_2)_4-$, R^3 = $-C\equiv C-SiMe_3$ **12**, 88%

7, R^1,R^2 = $-(CH_2)_4-$, R^3 = $-C\equiv C-Ph$ **13**, 91%

8, R^1,R^2 = $-(CH_2)_4-$, R^3 = CN **14**, 60%

9, R^1 = Me, R^2 = R^3 = H **15**, 24%, + **16**, 36%

10, R^1 = *i*Pr, R^2 = H, R^3 = $-C\equiv C-SiMe_3$ ---



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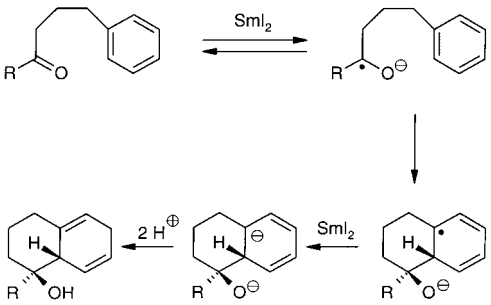
substituent. Of course, it also proved the constitution of compound **14** and the suggested connectivity pattern. We assume that the products **12** and **13** have the same configuration and extend this also to **11**, **15**, and the γ-lactone **16** derived from **15**.

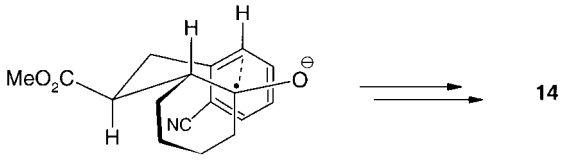
The following mechanism seems likely to us (Scheme 1). As expected for samarium diiodide promoted cyclizations a first (reversible) electron transfer generates a ketyl radical anion,[2, 3] which now attacks the aryl group in the *ortho* position.



Scheme 1. Proposed mechanism for the SmI_2-promoted cyclization of aryl ketones.

The resulting cyclohexadienyl radical is reduced to a cyclohexadienyl anion by a second electron transfer, and the anion is finally protonated in analogy to the Birch reduction.[10] It is not clear at the moment whether other steps of this sequence are reversible and whether a direct 6-cyclization (as formulated) occurs or a 5-cyclization to a spiro compound that is followed by a 1,2-shift. This should lead to two regioisomeric products since a priori two C–C bonds are able to undergo the 1,2-migration. Since only one product was obtained, this advocates against this (more complex) mechanism though it does not disprove it.

The configuration of the products is determined in the cyclization step. Thus, for the formation of tricyclic compound **14** we discuss the reactive conformation **17** for the ketyl radical anion. A chairlike folding, as suggested for most of the



17

intramolecular additions to C–C double bonds,[2] with substituents and the ketyl oxygen atom in equatorial positions is considerably favored over conceivable alternatives (e.g., the oxygen atom in an axial position). This model plausibly explains why cyclization of **10** is unsuccessful: The isopropyl group is too bulky to allow the aryl group to occupy a position at a proper distance. This picture illustrates why the second diastereomer of **8** did not react. The carbonyl group should be located equatorial-"exocyclic" in a corresponding conformation, and therefore it could not approach the aryl group.

It must be mentioned here that a related electrochemical reaction of γ-aryl ketones leads to the same type of products with identical relative configuration.[11] Similar conformative effects have been suggested for the observed stereochemistry. However, for aryl groups with electron-withdrawing substituents and for condensed aromatic compounds the reaction does not stop at the 1,4-cyclohexadiene stage, but further reduction provide cyclohexene and cyclohexane derivatives. The cathodic cyclization of pyridinium salts to quinolizidine and indolizidine derivatives, as reported by Schäfer et al.,[12] also involves subsequent reduction. In contrast, our samarium diiodide promoted cyclization seems to be redox selective. The examples investigated showed no sign of this type of subsequent reduction, which was most likely to occur during the transformation of **8** to **14**. Related to our experiments is the cyclization of samarium ketyls with arenetricarbonylchromium complexes, as described by Schmalz et al.[13] Here either a demetalated 1,3-cyclohexadiene derivative is formed or substituted arene$(CO)_3$ complexes are generated under formal displacement of a methoxy group.

The new reaction mode of samarium ketyls reported here should be of importance for various aspects: First, precursors incorporating aryl substituents, which should serve for other types of cyclization reactions, may react with the involvement of the aromatic group. Second, this reaction should have a high synthetic potential since 1,4-cyclohexadiene derivatives formed by this reductive alkylation may be interesting for many subsequent reactions. Thus, we are currently investigating the scope and limitations of this transformation and relevant mechanistic details. Of particular importance will be the substitution of HMPA by less dangerous additives.[14] The potential of this new reaction for the synthesis of carbocycles and heterocycles is demonstrated for example **18** with a naphthyl group as ketyl acceptor to give the tetracyclic compound **19** (characterized by X-ray analysis[9]) and a

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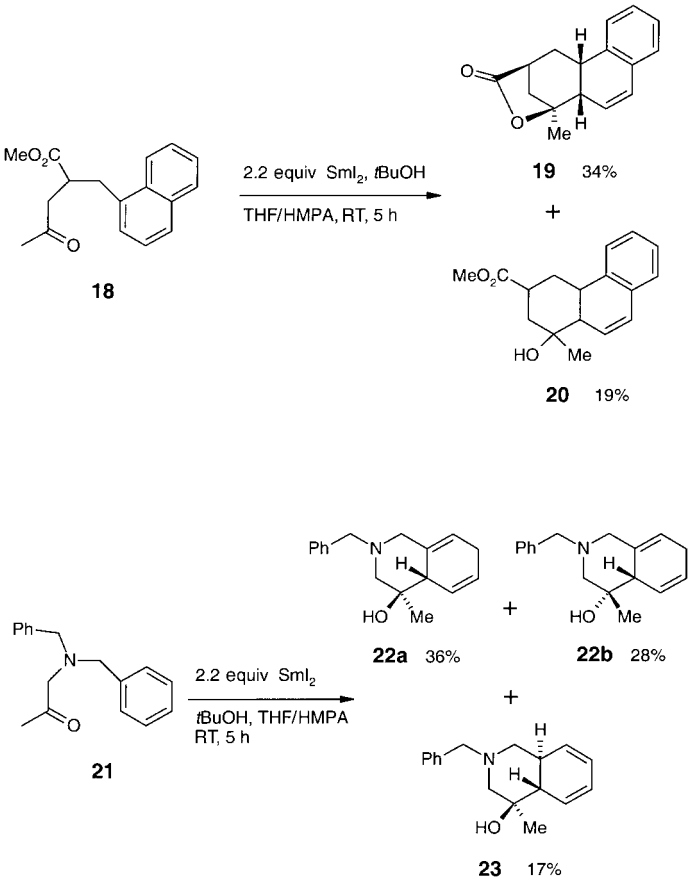
second compound **20** (configuration not yet defined), and for the reaction of *N*,*N*-dibenzyl-substituted amino ketone **21**, which produces isoquinoline derivatives **22** and **23**.



Experimental Section

In a typical experiment, a solution of 1,2-diiodoethane (0.270 g, 0.96 mmol) in anhydrous THF (20 mL) was added to samarium (0.160 g, 1.05 mmol) under an argon atmosphere. The reaction mixture was stirred for 1.5 h at room temperature, and the resulting deep blue solution was treated with HMPA (1.410 g, 7.88 mmol). Stirring was continued for 10 min, and argon was bubbled through the reaction mixture for a further 10 min. To the resulting solution was added a mixture of **8** (0.130 g, 0.44 mmol) and *t*BuOH (0.065 g, 0.87 mmol) in anhydrous THF (10 mL) over a period of 30 min. The mixture was then stirred for 4.5 h at room temperature, and a saturated solution (10 mL) of sodium bicarbonate was added. The organic layer was separated, the aqueous phase was extracted with diethyl ether (3×10 mL), and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and column chromatography of the crude product on silica gel (hexane/ethyl acetate 3/1) afforded **14** as colorless crystals (0.075 g, 60 %). M.p. 151 – 153 °C; ^{1}H NMR ($CDCl_3$): $\delta = 5.83$ (s, 2H; HC=CH), 3.72 (s, 3H; OCH_3), 3.99 (dd, $J = 4.1$, 13.5 Hz, 1H; CH_2), 2.89 (s, 3H; CH, CH_2), 2.79 (td, $J = 4.0$, 12.4 Hz, 1H; CH), 2.34 (t, $J = 13.5$ Hz, 1H; CH_2), 1.97 – 1.88 (m, 1H; CH), 1.56 – 1.43 (m, 7H; 3CH_2, OH), 1.38 – 1.30 (m, 2H; CH_2); ^{13}C NMR ($CDCl_3$): $\delta = 174.2$ (s, C=O), 150.9 (s, =C), 123.5, 122.4 (2d, HC=CH), 117.8 (s, =C), 104.7 (s, C≡N), 75.0 (s, C–OH), 52.0 (q, OCH_3), 50.0, 44.8, 43.3 (3d, 3CH), 36.0, 28.4, 28.0, 23.9, 20.9, 19.6 (6t, 6CH_2); IR (KBr): $\tilde{\nu} = 3515$ (br, O–H), 2940 – 2860 (C–H, =C–H), 2215 (C≡N), 1715 (C=O), 1640 cm^{-1} (C=C); elemental analysis calcd for $C_{17}H_{21}NO_3$ (287.4): C 71.05, H 7.36, N 4.87; found: C 71.10, H 7.58, N 4.85.

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Discovery and Optimization of Heterogeneous Catalysts by Using Combinatorial Chemistry**

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Solid catalysts are used in the manufacturing of a vast array of chemicals and fuels, and as such significantly contribute to our economy and high living standards.[1] In addition, catalysts provide important environmental benefits, such as in catalytic converters for automobiles. However, in spite of their significance and broad utility, the discovery of new catalysts continues to be an arduous and rather unpredictable trial-and-error process. Catalysts traditionally are developed by using a large variety of tedious, time-consuming, and often one at a time methods, characterized and tested for activity, modified,

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