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Samarium Diiodide-Induced Couplings of Carbonyl Compounds with Methoxyallene Leading to 4-Hydroxy 1-Enol Ethers

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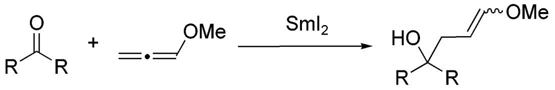
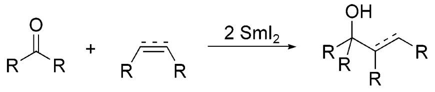
ABSTRACT



A surprising samarium diiodide-induced coupling reaction of carbonyl compounds with methoxyallene provided 4-hydroxy 1-enol ethers, which are versatile synthetic building blocks. In this coupling reaction, methoxyallene serves as an acrolein equivalent, which cannot directly be employed.

Samarium diiodide has received considerable attention in the past two decades. First introduced to synthetic organic chemistry by Kagan,[1] it has rapidly been established as a powerful one-electron-transfer reagent employed in many important transformations including various sequential reactions.[2] This is mainly attributed to its easy preparation, its applicability under mild and selective conditions, and the possibility of tuning its reactivity by assistance of catalysts and additives. Ketyl−olefin couplings represent one important class of samarium(II)-mediated transformations (Scheme 1), and reactions of various carbonyl compounds **1** with alkenes, alkynes, and arenes **2** have intensively been studied in recent years. The intramolecular versions lead to highly functionalized carbocycles and heterocycles, often in good yields and with outstanding diastereoselectivities.[3]

Scheme 1



1 **2** **3**

However, investigations with α,*β*-unsaturated aldehydes,[4] in particular with acrolein, but also with allenes,[5] are very rare. As part of our interest in samarium(II)-mediated ketyl−olefin coupling reactions,[3b,c] experiments were therefore carried out with diphenylallene **4** and methoxyallene **6**.

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[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, see: (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) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727−2751. (g) Hölemann, A. *Synlett* **2001**, 1497−1498.

[3] Selected recent references on samarium diiodide-induced ketyl-coupling reactions: (a) Schmalz, H.-G.; Kiehl, O.; Gotov, B. *Synlett* **2002**, 1253−1256. (b) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290−1292. (c) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem.* **1999**, *111*, 874−876; *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 789−791. (d) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872−882. (e) Ohno, H.; Maeda, S.; Okumura, M.; Wakayama, R.; Tanaka, T. *Chem. Commun.* **2002**, 316−317. (f) Kuo, Ch.-W.; Fang, J.-M. *Synth. Commun.* **2001**, *31*, 877−892.

[4] α,*β*-Unsaturated aldehydes have been employed in samarium(II)-induced iodomethylations and Mukaiyama−aldol reactions: Giuseppone, N.; Collin, J. *Tetrahedron* **2001**, *57*, 8989−8998. Imamoto, T.; Hatajima, T.; Takiyama, N.; Takeyama, T.; Kamiya, Y.; Yoshizawa, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127−3135. One cyclization of an α,*β*-unsaturated aldehyde to a triple bond leading to a pyrrolidine derivative was reported: Baldwin, J. E.; MacKenzie, S. C.; Moloney, M. G. *Tetrahedron* **1994**, *50*, 9425−9438.

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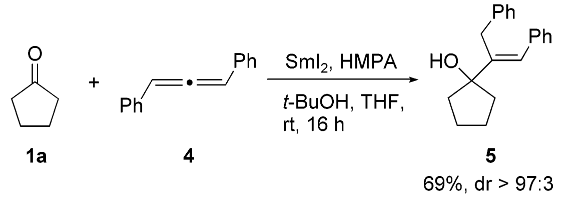
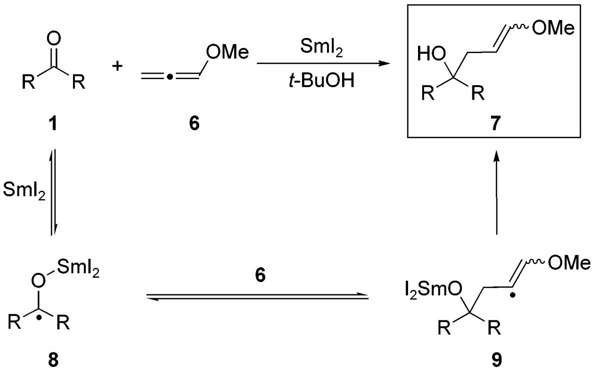
Allene **4** (1.1 equiv) reacted smoothly with cyclopentanone **1a** in the presence of samarium(II) iodide and HMPA (hexamethylphosphoramide) affording allylic alcohol **5** in good yield and excellent diastereoselectivity (Scheme 2). As expected, addition of the ketyl occurred to the central carbon of **4** due to the higher stability of the intermediate allyl radical. Small amounts of 1,3-diphenylpropene were isolated as a byproduct resulting from reduction of the allene moiety.

Scheme 2



We then turned our attention to the highly versatile C3-building block methoxyallene **6**.[6] Reaction of this allene with different carbonyl compounds proceeded under the same conditions; however, in contrast to allene **4**, coupling occurred at the terminal carbon of methoxyallene leading to 4-hydroxy 1-enol ethers **7** (Scheme 3). In accordance with literature reports,[3] we propose a ketyl radical anion **8** as the first intermediate that is generated by electron transfer of samarium diiodide to the carbonyl functionality. Addition to **6** then affords vinyl radical **9**, which is directly converted to **7** by abstraction of hydrogen from THF (or HMPA).[7] Although alkoxyallenes appear to be nucleophilic components at first glance, their terminal double bond has considerable electrophilic character and can therefore react smoothly with a nucleophilic radical such as the samarium ketyl.[8] In this novel coupling process, methoxyallene **6** serves as an equivalent of acrolein providing 4-hydroxy 1-enol ethers **7**, which are intermediates with a masked aldehyde functionality. They are versatile building blocks for further transformations which motivated us to investigate scope and limitations of the new coupling reaction.

Scheme 3



Generally, reductive couplings were conducted by addition of the THF solution of carbonyl component **1** (1.0 equiv), methoxyallene **6** (2.0 to 3.0 equiv), and *tert*-butyl alcohol (2.0 equiv) to the solution of freshly prepared samarium diiodide (2.2 equiv) and HMPA (18 equiv) in THF at room temperature. According to previous reports, HMPA was found to be essential for successful coupling as this cosolvent significantly increases the reduction power of samarium(II).[9,10] A variety of ketones was examined, and the results are summarized in Table 1. Products **7** were generally obtained as a mixture of (*E*)- and (*Z*)-isomers in ratios of 50:50 to 65:35. In most cases, the (*E*)-isomer was only slightly preferred.

First, cyclic ketones were combined with **6** under the described conditions. Cyclopentanone **1a** and cyclohexanone **1b** furnished the enol ethers **7a** and **7b** as the only isolated products in high yields. Starting with 4-*tert*-butylcyclohexanone, the enol ether **7c** was obtained in 58% yield, and 41% of starting material **1c** were recovered. Apparently, conversion of the ketone is not complete in this reaction which may also happen in other examples where unconsumed ketones could not be reisolated due to their volatility.[11]

With respect to the cyclohexane ring, product **7c** was formed as a single diastereomer (dr > 97:3). The configuration was identified by transferring **7c** into the corresponding lactone **13** (see Scheme 5). By comparing the data of **13** with that of the *cis* and *trans* isomers reported in the literature,[12] **7c** was clearly assigned to be the *trans* isomer. This result can be rationalized by assuming that the sterically demanding samarium alkoxy group and the *tert*-butyl group of the intermediate prefer equatorial positions before addition to **6**. Other substituents and even heteroatoms are also tolerated in the 4-position. Reaction of monoprotected 1,4-

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[5] One intramolecular coupling of electron-deficient allenyl aldehydes leading to vinyl-substituted cycloalkanols was reported: Gillmann, T. *Tetrahedron Lett.* **1993**, *34*, 607−610. Methoxyallene itself has only been used in a samarium(II)-mediated [3+2] cycloaddition with carbonyl ylides: Hojo, M.; Aihara, H.; Hosomi, A. *J. Am. Chem. Soc.* **1996**, *118*, 3533−3534.

[6] Reviews: (a) Zimmer, R. *Synthesis* **1993**, 165−178. (b) Reissig, H.-U.; Hormuth, S.; Schade, W.; Okala Amombo, M. G.; Watanabe, T.; Pulz, R.; Hausherr, A.; Zimmer, R. *J. Heterocycl. Chem.* **2000**, *37*, 597−606.

[7] Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943−961.

[8] Cuprates add to C-3 of alkoxyallenes: Marek, I.; Alexakis, A.; Mangeney, P.; Normant, J.-F. *Bull. Soc. Chim. Fr.* **1992**, *129*, 171−190.

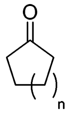
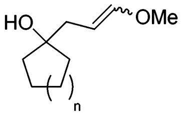
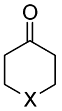
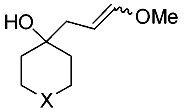
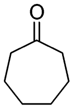
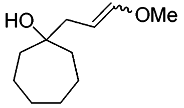
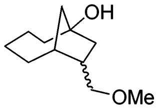
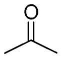
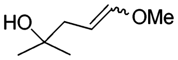
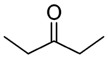
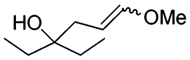
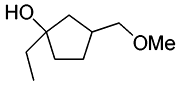
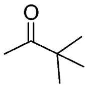
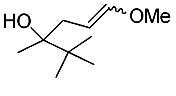
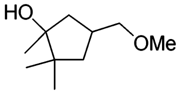
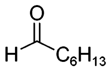
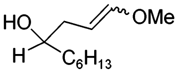
[9] (a) Inanaga, I.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485−1486. (b) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137−1140. (c) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6895−6899 and references cited therein.

[10] Attempts to replace HMPA by less toxic cosolvents have so far not been successful in general. In individual examples, related additives (e.g., *N*-methylpyrrolidinone or other phosphoramide derivatives) were efficient but unfortunately no rule has yet been recognized in which cases these additives are applicable. Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U., unpublished results.

[11] When the reaction was carried out in the presence of 4.2 equiv of SmI_2, only traces of the starting material **1c** were detected in the crude mixture. However, the yield of **7c** was not improved. Increasing the amount of **6** also gave unsatisfactory results, as **6** itself slowly reacts with SmI_2 yielding unidentifiable products. Addition of SmI_2 to a solution of **1c** and **6** slightly increased the yield of **7c**; however, 16% of starting material was again recovered.

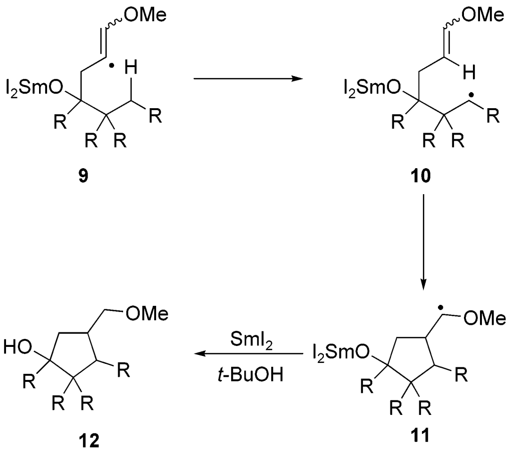
[12] Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669−1674.

Table 1. Samarium Diiodide-Induced Coupling of Methoxyallene **6** with Carbonyl Compounds **1**[a]

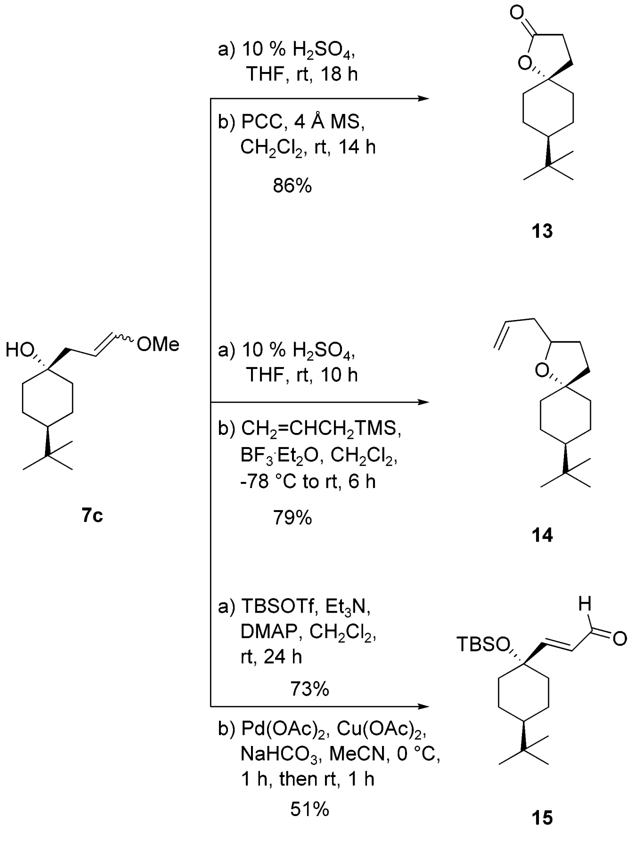
Starting material	Addition product[b]	Cyclization product[b]
		
1a n = 1	**7a** 85% (60:40)	—
1b n = 2	**7b** 79% (60:40)	—[c]
		
1c X = CH*t*-Bu	**7c** 58% (60:40),[d] dr > 97:3[e]	—[c]
1d X = C(OCH$_2$)$_2$	**7d** 54% (55:45)	—
1e = NBoc	**7e** 51% (50:50)[f]	—[g]
		
1f	**7f** 29% (60:40)	**12f** 34%, dr > 97:3
		—
1g	**7g** 26% (65:35)	
		
1h	**7h** 44% (55:45)[h]	**12h** 8%[h]
		
1i	**7i** 4% (50:50)[h]	**12i** 18%, dr > 97:3[h]
		—[c]
1j	**7j** 43% (55:45)	

[a] General conditions: **6** (2.0−3.0 equiv), SmI$_2$ (2.2 equiv), HMPA (18 equiv), *t*-BuOH (2.0 equiv), THF, rt, 16 h. [b] Yields for isolated products after chromatography. *E*/*Z* ratios are given in parentheses. [c] Traces of cyclopentanol **12** were detected in the crude mixture. [d] Reisolation of 41% starting material **1c**. [e] Only *trans* isomer was detected. [f] Isolation of 11% of secondary alcohol. [g] Small amounts of a bicyclic compound related to **12f** were obtained after chromatography. [h] **7** and **12** were isolated as mixture. Yield was calculated according to the ratio determined by ^{1}H NMR.

Scheme 4



Scheme 5



cyclohexadione **1d** and Boc-protected piperidinone **1e** with **6** furnished the corresponding products **7d** and **7e** in 54% and 51% yield, respectively.

In contrast, samarium diiodide-promoted reaction of **6** with cycloheptanone **1f** surprisingly resulted in the formation of two constitutional isomers. Separation by chromatography gave 29% of expected **7f** and 34% of bicyclic cyclopentanol derivative **12f**. Formation of cyclopentanol **12** can be rationalized by an intramolecular hydrogen atom transfer to vinyl radical **9** (Scheme 4) affording alkyl radical **10**,[13] which attacks the double bond of the enol ether leading to stabilized radical **11**. A second electron transfer of samarium diiodide followed by protonation finally yields cyclopentanol derivative **12**. Product **12f** was formed as a single diastereomer;

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[13] Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, pp 333−501.

however, the configuration of **12f** could so far not be assigned.

The change from cyclic compounds to acyclic ketones significantly decreased the yields of coupling product **7**. Starting with acetone, the corresponding adduct **7g** was isolated in only 26% yield, which may be due to the high volatility of the product. Applying the procedure to diethyl ketone **1h** considerably improved the mass balance (52% combined yield); however, a mixture of two isomers in a ratio of 85:15 was isolated. The major product was identified to be the expected **7h**, whereas the minor component was cyclopentanol derivative **12h**. Branched ketones such as pinacolone **1i** gave the desired products **7** even in lower yields. Only traces of the desired product **7i** with **12i** being the major isolated product of this reaction (22% yield) were isolated. Cyclopentanol **12i** was formed as a single diastereomer with a yet unknown configuration. It was also shown that even aldehydes can be employed in this coupling process. Reaction of heptanal with **6** yielded the corresponding adduct **7j** in moderate 43% yield. Aldehydes are generally more prone to simple reduction and pinacol coupling, which may diminish the efficiency of the desired coupling process.

We have demonstrated that various ketones and even aldehydes can be used in this novel coupling reaction. Whereas 5- and 6-membered cycloalkanones smoothly afforded 4-hydroxy 1-enol ethers **7** in moderate to good yields, the corresponding acyclic ketones gave lower yields and cyclopentanol byproducts **12**. Branched substituents or more flexible cyclic systems such as cycloheptanone led to formation of compounds **12** because a hydrogen transfer to the vinyl radical intermediate is possible through a geometrically favored six-membered transition state.

4-Hydroxy 1-enol ethers **7** are masked aldehydes and therefore useful building blocks for many transformations. Their versatility is demonstrated in Scheme 5 by different examples. Acidic hydrolysis of the enol ether unit with aqueous sulfuric acid followed by oxidation using PCC furnished γ-lactone **13**[12] in 86% yield over the two steps.

Reactions of γ-lactols (or their acetals) with silylated nucleophiles in the presence of Lewis acids furnish substituted tetrahydrofuran derivatives in good yields and very often with high diastereoselectivity.[14] Acidic hydrolysis of the enol ether moiety followed by treatment of the obtained lactol with allyltrimethylsilane in the presence of boron trifluoride etherate provided allyl-substituted spirocyclic compound **14** in 79% yield (with respect to **7c**). Other silylated nucleophiles such as triethylsilane and silyl enol ethers were similarly successful yielding the corresponding tetrahydrofurans in 64−81% yield.[15]

Alternatively, aldehydes may be synthesized from **7** and its derivatives. Thus, TBS-protection of the tertiary alcohol and subjection to palladium(II) acetate afforded the expected α,β-unsaturated aldehyde **15** in moderate yield as a single diastereomer.[16]

In conclusion, a variety of ketones could be coupled with methoxyallene **6** in the presence of samarium diiodide in moderate to good yields. Methoxyallene herein played the role of a masked equivalent for acrolein allowing a straightforward access to 4-hydroxy 1-enol ethers **7** accompanied in certain cases by cyclopentanols **12** as byproducts. Products **7** are highly versatile building blocks, and their applicability was demonstrated by different examples. Starting from cyclic ketones, spiro compounds were easily constructed. As a consequence of this surprising coupling reaction and the versatility of the products, the applicability of different allenes,[17] in particular substituted derivatives, is currently under investigation.

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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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(14) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893−3901 and references therein.

(15) Hölemann, A.; Reissig, H.-U., unpublished results.

(16) Takayama, H.; Koike, T.; Aimi, N.; Sakai, S. *J. Org. Chem.* **1992**, *57*, 2173−2176.

(17) When **1** was combined with a 3-alkyl-substituted methoxyallene derivative in the presence of SmI_2, no reaction occurred. Only starting material was reisolated by chromatography. However, 3-methoxy-1,2-butadiene furnished the expected addition product, albeit in very low yield.