Samarium(II) Iodide Promoted Intermolecular Ketone–Olefin Couplings Chelation-Controlled by α-Hydroxyl Groups

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Summary: The hydroxyl group directed *inter*molecular ketone–olefin coupling reactions induced by SmI_2 between α-hydroxyl ketones and α,β-unsaturated esters occurred with excellent stereochemical control about the newly formed asymmetric centers.

Samarium(II) iodide (SmI_2) has become an exceedingly reliable reagent for promoting reductive coupling reactions including ketone–olefin and pinacol couplings.[1] Much research has been directed toward the development of stereocontrolled carbon–carbon bond formation reactions promoted by SmI_2. In particular, intramolecular variants of these transformations proceeded stereoselectively to provide functionalized carbocycles in many cases.[2,3] In contrast, only one example of stereoselective *inter*molecular coupling induced by SmI_2 has been reported by Inanaga *et al.*[4,5] Previous research from this laboratory established that the stereochemical course of the intramolecular reductive coupling reactions mediated by SmI_2 is completely stereocontrolled by chelation of the Sm(III) cations attached to the resulting ketyl radicals with the hydroxyl groups incorporated within the starting materials.[3] The latter studies on the *inter*molecular version of the hydroxyl group directed ketone–olefin couplings revealed that the reactions between the α-hydroxy ketones and the α,β-unsaturated esters also take place with high stereocontrol about the new chiral centers. In this paper, we report these new types of highly stereoselective *inter*molecular carbon–carbon bond formation reactions promoted by SmI_2.

In the present study, the SmI_2-induced reductive couplings of (±)-3-hydroxy-5-phenyl-2-pentanone (**1**)[6] were carried out using various radical acceptors. As summarized in Scheme 1, the coupling reactions generally proceeded with high diastereoselectivity to provide the *syn*-1,2-diol products (**2**–**5**) in excellent yields. Apparently, the diastereofacial preference of the α-hydroxy ketone (**1**) was unaffected by changing the ketyl radical acceptor. At first, stereochemical control was examined by utilizing ethyl acrylate and acrylonitrile as the ketyl radical acceptors. The reductive coupling of **1** with ethyl acrylate produced the *syn*-γ-lactone **2**[7] along with a small amount of its *anti*-counterpart.[7] Interestingly, lowering the reaction temperature from 0 to −78 °C led to a drop in diastereoselectivity (*syn*:*anti* = 90:10→82:18).[8] When acrylonitrile was used for the reductive coupling of **1**, diastereoselection was enhanced. The diastereomeric ratio of the *syn*-diol **3**[7] to its *anti*-diastereoisomer[7] also increased to 99:1 when the coupling reaction was performed at 0 °C and a ratio of 92:8 was obtained at a reaction temperature of −78 °C. In the SmI_2-promoted coupling of **1** with ethyl crotonate and 2(5*H*)-furanone, excellent diastereoselectivity was achieved at three contiguous stereocenters to afford the *syn*-1,2-diol products, *syn*-γ-lactones **4**[9] and **5**,[9] respectively. Obviously, the geometry of the carbon-carbon double bond of ethyl crotonate and 2(5*H*)-furanone determines the relative stereochemistry between the two new stereogenic centers of **4** and **5**. Therefore, the facial preference of ethyl crotonate and 2(5*H*)-furanone in the SmI_2-mediated coupling of **1** is the same. The temperature dependence of diastereoselection, similar to that seen for the reactions with ethyl acrylate and acrylonitrile, was observed for the coupling of **1** with ethyl crotonate. In contrast, a decrease in reaction temperature resulted in increased stereoselectivity of the reductive coupling of **1** with 2(5*H*)-

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(6) (±)-3-Hydroxy-5-phenyl-2-pentanone (**1**) was prepared from 3-phenylpropionaldehyde in 53% overall yield by the sequence of (1) addition with $LiC{\equiv}CSiMe_3$, (2) desilylation, (3) acetylation of the hydoxyl group of 5-phenyl-1-pentyn-3-ol, (4) hydration of the acetylene group using $NaAuCl_4$ [Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729], and (5) hydroylsis.

(7) The *syn*-1,2-diol stereochemistry of the *syn*-γ-lactone **2** and the *syn*-diol **3** were assigned as follows. In the 2D-NOESY spectra of the 5-membered phenyl borate (1,3,2-dioxaborolane) of **3**, (4′*R**,5′*R**)-3-[4-methyl-2-phenyl-5-(2-phenylethyl)-1,3,2-dioxaborolan-4-yl]propiononitrile, NOE correlations were observed between C_4-Me and $C_{5'}$-CH_2 and between C_3-H_2 and $C_{5'}$-H. On the other hand, hydrolysis of the nitrile group of **3** afforded **2**. Similarly, the *anti*-1,2-diol stereochemistry of the minor diastereoisomers of **2** and **3** was established.

(8) The diastereomeric ratios were determined from the 400 MHz ^{1}H-NMR spectra of the mixture of the *syn*- and *anti*-1,2-diol products.[11]

(9) The relative stereochemical assignment of the *syn*-γ-lactone **4** was based on 2D-NOESY spectral data (*vide infra*) of **4** and the 5-membered phenyl borate (1,3,2-dioxaborolane) derived from **4**. In the 2D-NOESY experiment on (3*R**,4*R**,5*R**)-3,4-dimethyl-5-hydroxy-7-phenyl-4-heptanolide (**4**), C_3-H gave an NOE correlation peak with C_5-H, while C_3-Me also gave an NOE with C_4-Me. In addition, 2D-NOESY analysis of (3*R**,4′*R**,5′*R**)-3-[4-methyl-2-phenyl-5-(2-phenylethyl)-1,3,2-dioxaborolan-4-yl]-1-butanol revealed that NOE correlations were observed between $C_{4'}$-Me and $C_{5'}$-CH_2 and between C_3-H and $C_{5'}$-H. Analogous 2D-NOESY experiments on the isomeric γ-lactone and 5-membered phenyl borate prepared from the *syn*-γ-lactone **5** confirmed the relative stereochemistry of **5**.

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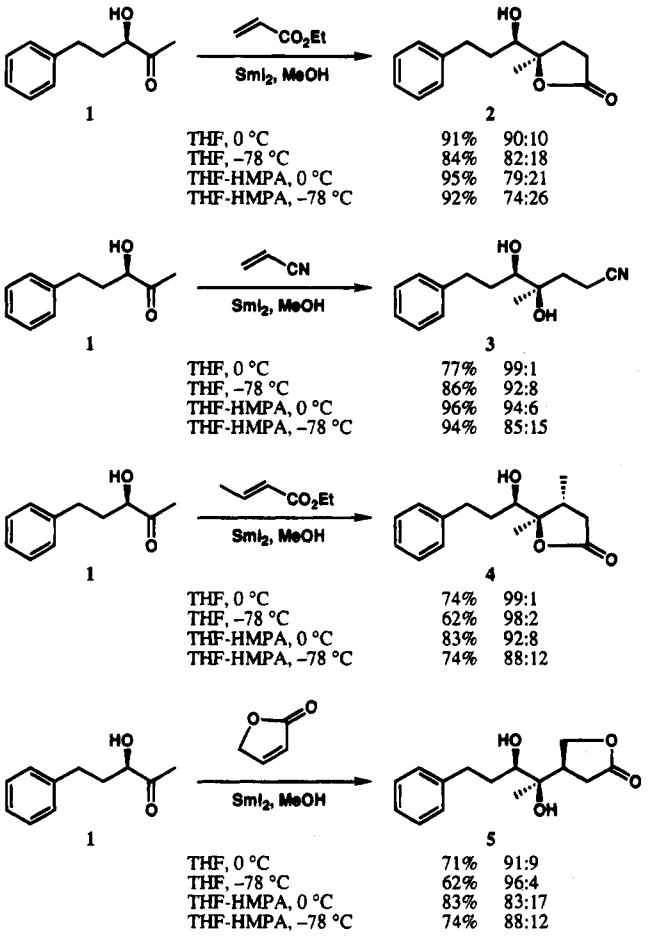
Scheme 1



furanone.[10] Thus, **4** and **5** were obtained in a products ratio (*syn*:*anti*)[11] of 99:1 and 96:4 when carrying out the reactions with ethyl crotonate and 2(5*H*)-furanone at 0 and −78 °C, respectively. It is noteworthy that the almost single stereochemical results were obtained from four possible products. Optimum reaction conditions for these ketone-olefin couplings involved the addition of a 0.1 M solution of SmI_2 in tetrahydrofuran (THF) (2.5 equiv) to a solution of **1**, methanol (5 equiv), and ethyl acrylate, acrylonitrile, ethyl crotonate, or 2(5*H*)-furanone

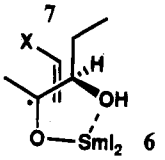


Figure 1.

(10 equiv) in THF at 0 or −78 °C. Reactions run in the presence of hexamethylphosphoramide (HMPA) resulted in some depression of the diastereoselection in all cases.

The observed *syn*-1,2-diol stereochemistry of the reaction products (**2**–**5**) can be explained by assuming a chelation control model as illustrated in Figure 1. Thus, after single-electron transfer from SmI_2 to the ketone functionality of **1**, chelation of the Sm(III) cation generated during the initial reduction process with the α-hydroxyl group constructs the five-membered ring ketyl radical **6**. The olefin **7** [ethyl acrylate, acrylonitrile, ethyl crotonate, or 2(5*H*)-furanone] approaches from the sterically less hindered face of **6** to form the carbon–carbon bond with high stereocontrol. Furthermore, when (±)-3-acetoxy-5-phenyl-2-pentanone and (±)-3-[(*tert*-butyldimethylsilyl)oxy]-5-phenyl-2-pentanone prepared from **1** were subjected to reduction by SmI_2 with ethyl acrylate, acrylonitrile, ethyl crotonate, or 2(5*H*)-furanone, reductive removal of the acetoxyl and (*tert*-butyldimethylsilyl)-oxyl groups always took place and the only product isolated was 5-phenyl-2-pentanone. Therefore, the α-hydroxyl group of **1** plays a definitive role in these coupling reactions induced by SmI_2.

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Supplementary Material Available: Typical experimental procedures for the SmI_2-induced reductive couplings as well as physical and spectroscopic data for compounds **2**–**5** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) Although the SmI_2-induced couplings of the α-hydroxyl ketone **1** with ethyl acrylate, acrylonitrile, and ethyl crotonate were complete within 5 min at 0 °C utilizing the optimized reaction conditions, the starting material **1** was consumed after 3 h under identical conditions when 2(5*H*)-furanone was used as the ketyl radical acceptor. The anomalous temperature dependence of the reaction with 2(5*H*)-furanone may be ascribed to the low reactivity of 2(5*H*)-furanone.

(11) In each case of the SmI_2-promoted coupling reactions of the α-hydroxyl ketone **1** with ethyl crotonate and 2(5*H*)-furanone, a small amount of another diastereomeric γ-lactone was obtained along with the *syn*-γ-lactone **4** or **5**, respectively. While these minor diastereoisomers possessed the *anti*-1,2-diol stereochemistry, the relative configuration about the two new stereocenters was the same as that of the *syn*-counterparts **4** and **5**, respectively. The relative stereochemistry of the *anti*-γ-lactones was verified by 2D-NOESY experiments similar to those performed in the stereochemical assignment of **4** and **5**.[9]