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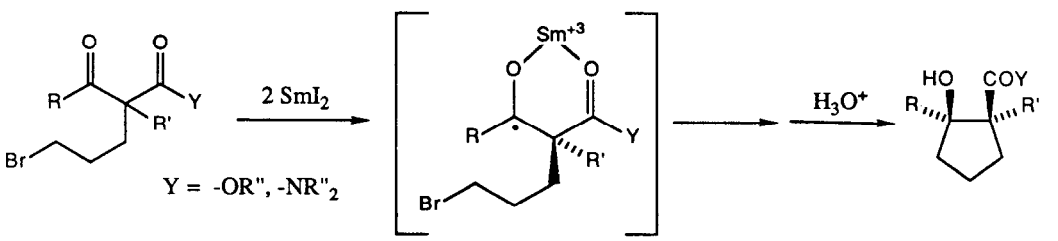
STEREOCONTROLLED INTRAMOLECULAR KETONE-OLEFIN REDUCTIVE COUPLING REACTIONS PROMOTED BY SAMARIUM DIIODIDE[1]

Gary A. Molander[2] and Caryn Kenny*

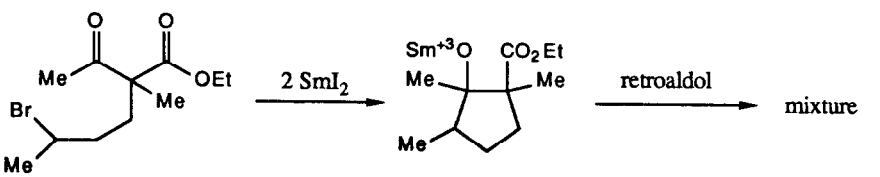
Department of Chemistry and Biochemistry, University of Colorado
Boulder, Colorado 80309-0215

Abstract: The stereocontrolled intramolecular coupling of unsaturated β-ketoesters and β-ketoamides is reported. Good yields of highly substituted β-hydroxycyclopentanecarboxylates are generated in the process, with substantial and predictable stereochemical control at three contiguous stereocenters.

We recently described stereocontrolled cyclizations of 2-(ω-haloalkyl)-β-ketoesters and 2-(ω-haloalkyl)-β-ketoamides mediated by samarium diiodide (SmI_2).[3] Utilizing this process, highly functionalized five- and six-membered ring carbocycles can be rapidly constructed in a stereocontrolled fashion. Our work,[3,4] reinforced by mechanistic studies of Kagan and coworkers,[5] indicated that the mechanism of these reactions involves initial electron transfer from SmI_2 to the β-dicarbonyl substrate, generating a ketyl. The observed stereochemistry is established by chelation of the Sm^{+3} ion generated in the process to the ester or amide carbonyl. Subsequent carbon-carbon bond formation leads to the observed products.



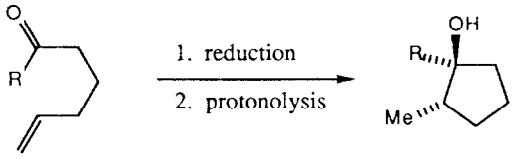
One limitation of this process is that secondary halides are unsuitable substrates for the reaction.[3] Thus, under aprotic reaction conditions required for this coupling reaction, a retroaldol reaction transpires which serves to rapidly drain off the desired cyclized aldolate intermediate.



As a means to further establish the mechanism of samarium diiodide-promoted reductive cyclization reactions, as well as to investigate related stereocontrolled intramolecular reactions, we sought to explore use of SmI_2 in mediating intramolecular ketone-olefin reductive coupling

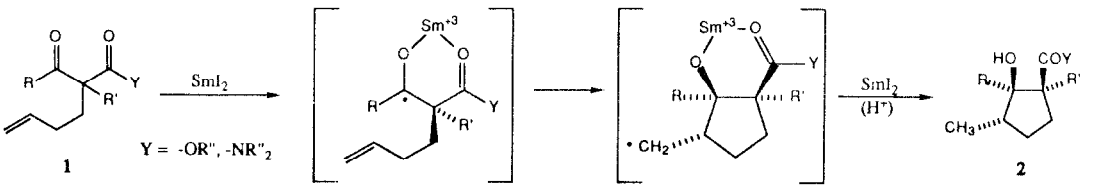
reactions. Studies of similar reactions have been reported previously under a variety of conditions. For example, electroreductive,[6] photoreductive,[7] as well as metal-induced ketone-olefin cyclizations[8] have all been explored. In addition, ketone-alkyne[8a,9] and ketone-allene coupling reactions[10] have received much attention.

Many of the ketone-olefin reductive cyclization processes cited above occur with significant (>10 : 1) stereochemical control at two stereocenters.[6a,c,7]



The source of this stereoselectivity has been ascribed to favorable secondary orbital interactions between the developing methylene radical center and the alkyl group of the ketyl,[6c,8a,11] and/or to electrostatic interactions in the transition state.[6a,7,11] We sought to take advantage of this inherent stereoselectivity, and to extend stereochemical control to a third stereocenter through chelation control by utilizing SmI_2 as the reductant in ketone-olefin reductive cyclizations (Scheme).

SCHEME



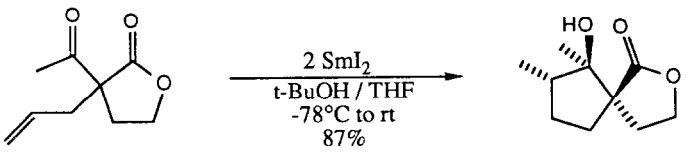
Towards this end, a variety of unsaturated β-ketoesters and β-ketoamides (1) were treated with two equivalents of SmI_2 and *t*-BuOH (~ 2 equiv.) in THF at -78°C. Upon warming to room temperature and quenching with a pH 8 phosphate buffer, the desired products (2) could be isolated by Kugelrohr distillation or flash chromatography in reasonable yields (Table).

TABLE. Intramolecular Reductive Coupling of Unsaturated β-Dicarbonyl Substrates (1)

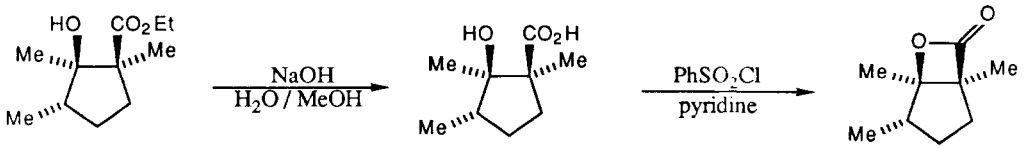
Substrate	Y	R	R'	% Isolated Yield (2)	Diastereoselectivity
1a	OEt	Me	Me	75	25 : 1
1b	OEt	Et	Me	66	30 : 1
1c	OEt	*i*-Pr	Me	63	30 : 1
1d	NEt_2	Me	H	78	>200 : 1
1e	NMe_2	Et	H	35	>120 : 1
1f	NMe_2	*i*-Pr	H	0	-

Although the amides appear to be especially sensitive to steric effects, ester substrates provide good yields throughout the series examined. Crude reaction mixtures were subjected to analysis on two different fused silica capillary gas chromatographic columns and by GC/MS. Diastereoselectivity was uniformly high (> 25 : 1), with only two diastereomers detected in most cases, and a single diastereomer detected in the remaining examples.

In addition to isolated rings, spirocyclic systems can also be generated.



Stereochemistry of the spirocyclic product was established by single crystal X-ray diffractometry. For products outlined in the Table, stereochemistry was confirmed by a combination of spectroscopic (NMR and FT-IR) and chemical techniques. For example, **2a** could be hydrolyzed to the corresponding β-hydroxy acid, then treated with benzenesulfonyl chloride in pyridine to generate a β-lactone.[12] This sequence established relative stereochemistry of the hydroxyl and carboxylate groups.



NOE difference spectroscopy[13] of **2a** allowed stereochemical assignment of all three methyl substituents on the same face of the molecule, thereby confirming the overall structure of the molecule.

We are in agreement with previous investigators[6c] on the general mechanism of these ketone-olefin coupling reactions. Since two equivalents of SmI_2 are required for the reaction, the reductive coupling must be a two electron process overall (Scheme). Cyclization would appear to occur after transfer of a single electron, with the Sm^{+3} ion controlling stereochemistry at this stage via chelation with the Lewis basic carbonyl. Subsequent reduction followed by protonolysis provides the observed products. Under these protic reaction conditions, the retroaldol process described above occurs extremely slowly. This allows isolation of more highly substituted products not accessible through secondary halide-ketone reductive cyclizations promoted by SmI_2 under aprotic conditions.

The SmI_2-promoted reductive cyclization of olefinic β-ketoesters and β-ketoamides thus provides a very efficient entry into highly functionalized cyclopentane derivatives with substantial control of stereochemistry over three centers. It also provides further support for the mechanism of stereocontrolled, SmI_2-mediated reactions. Other unsaturated ketone substrates are under current investigation, and show great promise for stereocontrolled generation of highly functionalized ring systems by SmI_2-promoted reductive cyclization reactions.

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