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Novel and stereoselective methods for the preparation of aromatic lactams via reductive coupling reactions mediated by SmI_2

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Abstract

Samarium(II) diiodide-mediated reductive cross-coupling of *N*-alkylated phthalimides with carbonyl compounds is shown to afford hydroxylated α-hydroxylactams. Ketoamides obtained by dehydration of these compounds through keto-enol tautomer isomerization were reduced with $NaBH_4$ in a completely stereoselective manner in the presence of $CeCl_3$ to give *threo*-aromatic lactams as the sole product. Direct reductive deoxygenation of these α-hydroxylactam intermediates with Et_3SiH in the presence of Lewis acid also displayed high stereoselectivity to afford the same *threo*-lactams exclusively. The mechanistic origins of this stereoselectivity are briefly documented.

Keywords: cross-coupling reaction; samarium(II) diiodide; cyclic imide; stereoselective reduction; deoxygenation.

Since its introduction by Kagan et al.[1] samarium(II) diiodide has been extensively investigated as a powerful electron donor able to promote a wide range of reduction and coupling reactions.[2] Its use in synthesis has been especially advantageous for ring closure reactions and C–C bond formation such as hydroxyl-directed addition of carbonyl to C=C double bond and stereocontrolled intramolecular pinacol reactions.[2d,3] The reactions of acid chlorides[4] and acid anhydrides[5] with this reagent have also been researched. In addition, intramolecular and intermolecular Barbier-type reactions mediated by SmI_2 have recently been reported;[4b,6] however, the complete lack of any study concerning the reactivity of samarium(II) compounds towards cross-coupling of cyclic imides with carbonyl subunits is surprising.

As part of our work designed to explore the use of these imides, we have demonstrated some significant stereoselective reactions[7] and their applications to the total syntheses of biologically active natural products.[8] The purpose of the present communication is to describe the result that *N*-alkylated phthalimides underwent fast reductive cross-coupling reactions with carbonyl compounds mediated by SmI_2 to provide pinacol-type α-hydroxylactams with a hydroxyl-containing alkyl side chain, and reduction of the corresponding ketoamides, derived from dehydration of the coupling products, with $NaBH_4$ in the presence of $CeCl_3$ occurred with extremely high stereoselectivity, leading to the *threo*-isomer as

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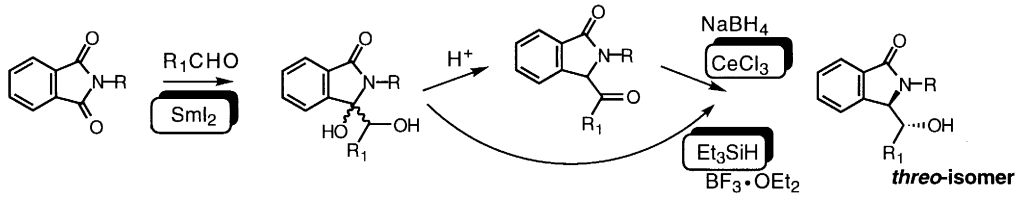
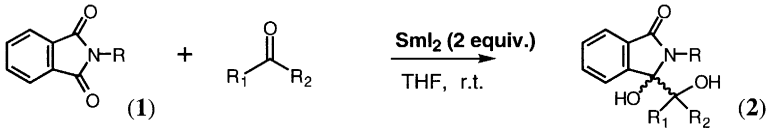
the sole product. Furthermore, exclusively *threo*-selective conversion of quaternary α-hydroxylactam intermediates was also accomplished directly with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ (Scheme 1). The mechanistic aspects of these reactions were also investigated.



Scheme 1.

Initial experiments have been performed on a reductive cross-coupling reaction mediated by SmI_2 between *N*-benzylsuccinimide and propanal with a variety of additives such as HMPA, $CuCl_2$, $FeCl_3$, or NiI_2.[6b] The reactions, however, did not proceed under any conditions except for the self-coupling of propanal. Next, we examined the same type of reactions employing aromatic imides. Whereas the coupling reactions of *N*-H- and *N*-phenylphthalimides with propanal gave inseparable mixtures even in the absence of an additive, respectively, use of the *N*-methyl derivative dramatically changed the results and rapidly brought about the desired coupling products **2** in satisfactory yields (Table 1, entries 1, 2). Furthermore, it became apparent that this procedure was applicable for the production of a wide range of reductive cross-coupling compounds employing *N*-benzyl- and *N*-naphthylphthalimides and ketones as well as aldehydes as a carbonyl unit (entries 3–10). Although the reason why such coupling products were obtained only by the use of aromatic *N*-alkylimides has not yet been clarified, it could depend on the capability of these imides to trap the ketyl samarium radical intermediates.



(**1**) (**2**)

Table 1
Reductive coupling of imides (**1**) with carbonyl compounds mediated by SmI_2

entry	R (imide (**1**))	R_1	R_2 [a)]	yield of (**2**) (%) [b)]
1	CH_3	CH_3CH_2	H	60
2	CH_3	$CH_3(CH_2)_5$	H	57
3	CH_2Ph	CH_3CH_2	H	79
4	CH_2Ph	$CH_3(CH_2)_5$	H	67
5	CH_2Ph	$Ph(CH_2)_2$	H	77
6	$CH(CH_3)$-1-Naphthyl	CH_3CH_2	H	44
7	$CH(CH_3)$-1-Naphthyl	$CH_3(CH_2)_5$	H	41
8	$CH(CH_3)$-1-Naphthyl	$Ph(CH_2)_2$	H	40
9	CH_2Ph	CH_3	CH_3	43
10	CH_2Ph	CH_3	$CH_3(CH_2)_2$	39

a) 2~5 equiv. of carbonyl compounds were used. b) Isolated yield.

In light of the above outcome, we turned our attention to the utilization of these pinacol-type compounds. To begin with, treatment of **2** with *p*-TsOH in benzene at 60°C provided the interesting ketoamides **3** in high yields in each case (Table 2). These could be derived from keto-enol isomerization

after dehydration. Since the stereodefined construction of *threo*- or *erythro*-heterocyclic moieties with a hydroxyl-containing side chain attracts considerable attention due to their presence in the framework of natural products,[9] we examined stereoselective reduction of **3**. As shown in Table 2, reduction of the *N*-methyl derivative **3a** with $NaBH_4$ only in MeOH gave the corresponding alcohols, *threo*-**4a** and *erythro*-**5a**, as a non-stereoselective mixture[10] (55:45) in a quantitative yield (entry 1). Even in the presence of metal halides such as $MgBr_2$ and $CeCl_3$[8a] remarkable enhancement of the selectivity was not observed (entries 2 and 3). Replacement of the *N*-methyl group by the larger benzyl function also had no effect as shown in entries 4 and 5. On the contrary, the use of $CeCl_3$ in the reduction of the *N*-benzyl compound **3b** surprisingly and dramatically changed the selectivity to yield *threo*-**4b** as the sole product (entry 7). The beneficial effect of $CeCl_3$ on this reduction was again established in reactions employing other ketoamides (entries 8 and 9).

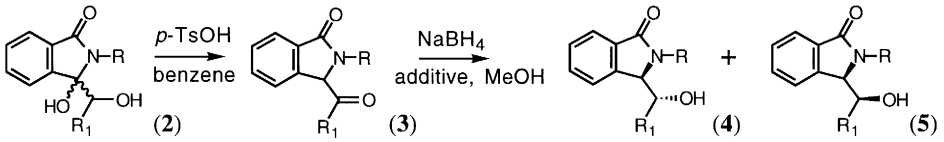


Table 2
Dehydration of (**2**) and stereoselective reduction of ketoamides (**3**) in the presence of metal halides

entry	(**2**) R	(**2**) R_1	a) yield of (**3**) (%)	b) additive	temp. (°C)	a) yield of reduction (%)	c) ratio of (**4**) : (**5**)
1	CH_3	$CH_3(CH_2)_5$	99 (**3a**)	---	r.t.	99	55 45[d]
2	CH_3	$CH_3(CH_2)_5$		$MgBr_2$	-40	72	50 50[d]
3	CH_3	$CH_3(CH_2)_5$		$CeCl_3$	-40	99	65 35[d]
4	CH_2Ph	$CH_3(CH_2)_5$	77 (**3b**)	---	r.t.	89	37 63
5	CH_2Ph	$CH_3(CH_2)_5$		$MgBr_2$	-40	72	42 58
6	CH_2Ph	$CH_3(CH_2)_5$		$SmCl_3$	-40	98	82 18
7	CH_2Ph	$CH_3(CH_2)_5$		**$CeCl_3$**	-40	61	**>99 <1**
8	CH_2Ph	CH_3CH_2	99 (**3c**)	**$CeCl_3$**	-40	88	**>99 <1**
9	CH_2Ph	$Ph(CH_2)_2$	89 (**3d**)	**$CeCl_3$**	-40	81	**>99 <1**

a) Isolated yield. b) 2~5 equiv. of metal halides were used.
c) Isolated ratio after chromatographic separation. d) Determined by ^1H NMR.

Next, we examined the direct conversion of quaternary α-hydroxylactams **2** to deoxygenated aromatic lactams. After unsuccessful attempts to obtain the hydrogenated products **4** or **5** under several conditions such as treatment with H_2 on Pd/C[11] or $NaBH_3CN$ in acidic medium,[12] we found that the use of *N*-methyl derivative with Et_3SiH in the presence of $BF_3 \cdot OEt_2$[8c] underwent fast reaction to afford the corresponding deoxygenated products *threo*-**4** and *erythro*-**5** (Table 3, entry 1) with moderately diastereofacial differentiation (79:21). After investigation of a variety of conditions, a surprising enhancement in stereoselectivity was finally observed upon employing the largest *N*-naphthylethyl group, leading to the *threo*-isomers **4** as the sole product (entries 3–5).

The same observed stereochemical outcome of these two reactions can be explained as follows, respectively: In the former, the reaction progressed through attack of $NaBH_4$ on the carbonyl group from the top face of the *cis*-fused metal–chelate in the reactions with $CeCl_3$ due to shielding of the bottom face by the large benzyl group, leading to exclusive formation of the corresponding *threo*-isomers (Fig. 1, Model A). On the other hand, in the Lewis acid-mediated deoxygenation the fact that increasing the

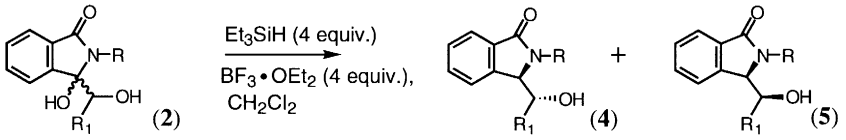


Table 3
Stereoselective hydrogenation of α-hydroxyaromatic lactams (**2**)

entry	(**2**) R	(**2**) R_1	temp. (°C)	a) yield of reduction (%)	b) ratio of (**4**) : (**5**)
1	CH_3	CH_3CH_2	-40~0	83	79 21[c]
2	CH_2Ph	CH_3CH_2	-40~0	59	92 8
3	$CH(CH_3)$-1-Naphthyl	CH_3CH_2	-40~-20	53	**>99** **<1**
4	$CH(CH_3)$-1-Naphthyl	$CH_3(CH_2)_5$	-40~-20	49	**>99** **<1**
5	$CH(CH_3)$-1-Naphthyl	$Ph(CH_2)_2$	-40~-20	44	**>99** **<1**

a) Isolated yield. b) Isolated ratio after chromatographic separation. c) Determined by ^{1}H NMR.

steric bulkiness of the nitrogen-protecting group clearly leads to an increase in *threo*-selectivity can be ascribed to the attack of Et_3SiH on the iminium ion intermediate from the bottom face of the non-chelation structure. This occurs due to the shielding effect of the three faces by the alkyl function and the two large groups of the alkoxyborane complex and *N*-substituent, which occupy positions furthest away from each other (Model B).

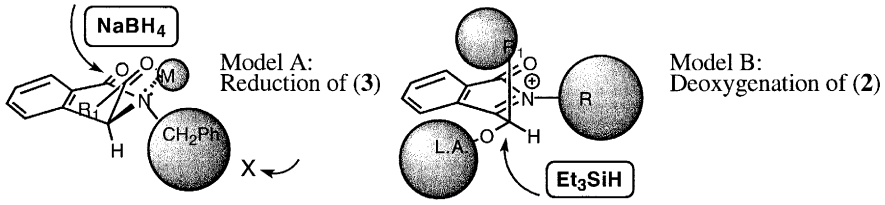


Fig. 1. Mechanistic origins of the stereoselective reduction of (**3**) and direct deoxygenation of (**2**)

In summary, we have disclosed herein the first example of samarium(II) diiodide-mediated coupling reaction of *N*-alkylphthalimides with carbonyl compounds. The use of $CeCl_3$ in the $NaBH_4$-reduction enabled complete *threo*-selective reduction of the ketoamides derived from dehydration of these adducts. Furthermore, direct hydrogenation of quaternary α-hydroxyl compounds also led to the *threo*-lactams with extremely high selectivity. This procedure will find application in the synthesis of some natural products.

Acknowledgements

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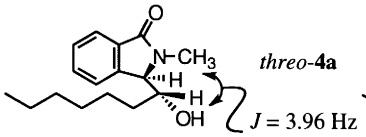
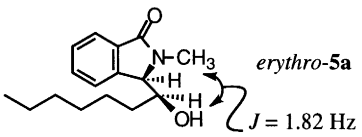


threo-**4a**

J = 3.96 Hz



erythro-**5a**

J = 1.82 Hz

Observed coupling constants of the other reduction products were almost identical with those of *threo*-**4a** and *erythro*-**5a**, respectively.

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