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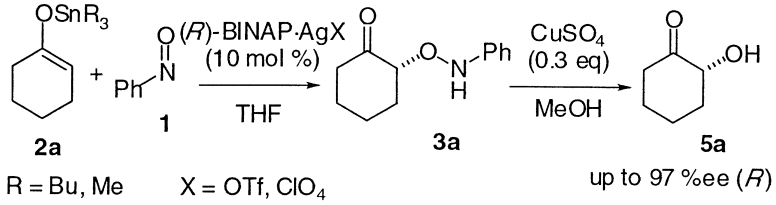

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Catalytic Enantioselective Synthesis of α-Aminooxy and α-Hydroxy Ketone Using Nitrosobenzene

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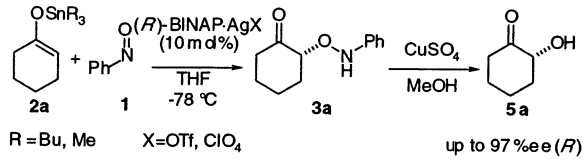
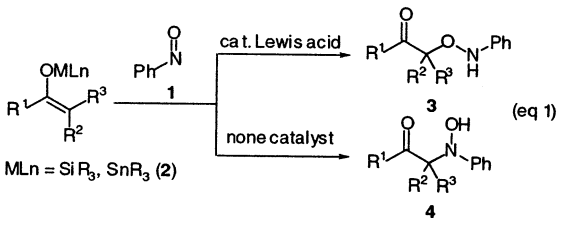
The stereoselective synthesis of α-hydroxy carbonyl compounds is a topic of interest as these structures are found in numerous important natural products; the importance has motivated the investigation of a wide variety of reactions to diastereoselective and enantioselective synthesis.[1] The asymmetric α-hydroxylation of enolates and enol derivatives is one of the simplest and most frequently used methods.[2] Despite considerable research,[3] the ultimate goal of developing a practical and highly effective catalytic system for enantioselective hydroxylation has remained elusive. Here we describe the catalytic enantioselective introduction of an oxy group at the α-position of ketone enolates using nitrosobenzene[4] and the synthesis of chiral α-hydroxy ketone in up to 97% ee (Scheme 1).

Scheme 1

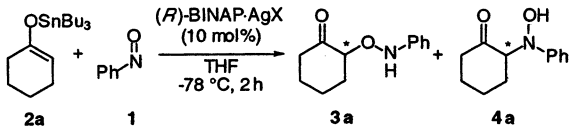


The present study sprang from our own earlier findings involving the reaction of nitrosobenzene (**1**) and silyl enolate which provided the aminooxy ketone **3**,[5] while the reaction of nitrosobenzene and silyl or tin enolate **2** without any Lewis acid catalyst led to the sole production of the hydroxyamino ketone **4** (eq 1).[6] From this



starting point, a highly enantioselective reaction of tin enolate **2** and nitrosobenzene has been developed in the presence of BINAP and AgOTf[7] (10 mol %, −78 °C, in THF) to furnish the aminooxy ketone **3a** in 91% ee and with high *O*-selectivity[8] (Table 1, entry 1). The (*R*)-BINAP·Pd$(ClO_4)_2$[9]-catalyzed reaction also generally afforded *O*-adduct, giving a highly regioselective reaction with an even slightly higher enantioselectivity. Of the various silver salts surveyed, the AgOTf and the $AgClO_4$ complex provided superior levels in both asymmetric induction and regioselection, affording **3a** (Table 1, entry 2), while the $AgSbF_6$ and AgOAc were more reactive and had comparable enantioselectivity, but less regioselectivity in comparison. The other metal catalysts including copper complexes were not catalytically active in providing *O*-adduct.

Table 1. (*R*)-BINAP−Silver Complex-Catalyzed Nitroso Aldol Reaction of Tin Enolate **2a** with Nitrosobenzene[a]



entry	AgX	yield, %[b]	3a/4a	ee, %[c]	
1	AgOTf	88	>99/1	**3a**: 91	**4a**: n.d.[d]
2	$AgClO_4$	95	>99/1	**3a**: 95	**4a**: n.d.
3	$AgBF_4$	64	>99/1	**3a**: 54	**4a**: n.d.
4	$AgNTf_2$	78	88/12	**3a**: 63	**4a**: 3
5	$AgSbF_6$	85	81/19	**3a**: 87	**4a**: <1
6	$AgPF_6$	86	80/20	**3a**: 76	**4a**: <1
7	AgOAc	82	72/28	**3a**: 87	**4a**: 23

[a] Reactions were conducted with 10 mol % (*R*)-BINAP·AgX, 1.0 equiv of nitrosobenzene, and 1.0 equiv of **2a** in THF at −78 °C for 2 h. [b] Isolated yield of two isomers. [c] Determined by HPLC (Supporting Information). [d] n.d. = not determined.

In an effort to expand the scope of the reaction, the tin enolates[10] of various carbonyl compounds were next investigated. Both the *O*-regioselectivity and the enantioselectivity were maintained for a range of alkyl- and phenyl-substituted tin enolates (Table 2, entries 7−13). The reaction took place equally well with any variation in cyclic tin enolate (Table 2, entries 1−6, 15−17). Although the tin enolate exists in the *O*-Sn form and/or *C*-Sn form, the *O*-Sn form was found to be much more reactive for this process. As compared to trimethyl tin enolates, tributyl tin enolates proved to have slightly increased *N*-selectivity under these conditions. To evaluate the relative reactivity of trimethyl tin substrate with tributyl tin substrate, 1 equiv of nitrosobenzene and a 1:1 mixture of these two alkyl tin enolates (**2a** and **2d**) were subjected to a competitive experiment in the absence of catalyst (eq 2). Tributyl tin enolates provided *N*-adduct in 78−79% yield, while trimethyl tin enolates afforded only 21−22% of *N*-adduct. This could explain the significant amount of uncatalyzed process that proceeds with tributyl tin enolate, which increases the N selectivities as compared to that with trimethyl tin enolate (entries 11,12 and 15,16).

The transformation of α-aminooxy ketone to α-hydroxy ketone is smooth and facile. Thus, the cleavage of the N−O bond in aminooxy ketone **3a** with a catalytic amount of copper sulfate afforded the α-hydroxy ketone **5a** in 94% yield without loss of enantioselectivity. As a more efficient procedure, after addition of **2a** to nitrosobenzene **1**, followed by treatment with a catalytic amount of copper sulfate and excess MeOH, α-hydroxy ketone **5a** was isolated as a single enantiomer in 93% yield and 97% enantiomeric excess (eq 3).

In conclusion, we have developed a highly catalytic, enantioselective process for the synthesis of α-aminooxy and α-hydroxy ketone. This study expands the scope of the enantioselective addition

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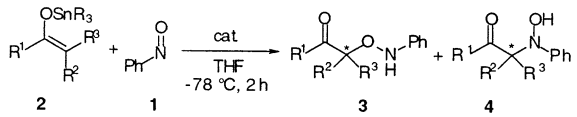
Table 2. Nitroso Aldol Reaction Using Various Tin Enolates **2a**−**2h**[a]

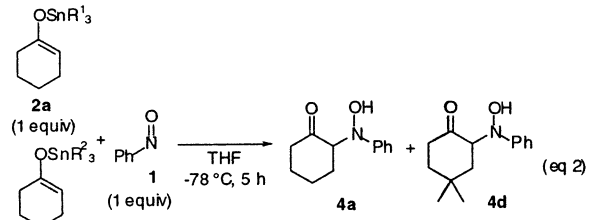


2 1 3 4

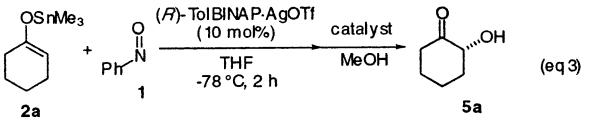
entry	enolate	cat. (mol%)[i]	R	yield,%[j]	3 / 4	ee,% of 3[k]
1[b, g]		A (10)	Bu	95	>99 / 1	95
2[b, g]	OSnR6	B (10)	Bu	92	>99 / 1	91
3[b, g]		C (10)	Bu	93	>99 / 1	92
4[b, h]		B (10)	Me	95	>99 / 1	97
5[b, h]	2a	C (10)	Me	94	>99 / 1	94
6[b, h]		B (2)	Me	78	>99 / 1	96
7[b, g]	OSnR3 Ph	A (10)	Bu	97	85 / 15	91
8[b, g]		C (10)	Bu	97	83 / 17	95
9[b, h]		B (10)	Bu	96	>99 / 1	95
10[b, h]	2b	C (10)	Me	97	>99 / 1	88
11[b, h]	OSnR6	B (10)	Me	94	>99 / 1	87
12[b, g]	2c	C (10)	Bu	90	66 / 34	85
13[b, h]	OSnR6 2d	B (10)	Me	92	>99 / 1	90
14[b, h]	OSnR3 2e	C (10)	Me	96	>99 / 1	85
15[c, e, h]	OSnR3	B (10)	Me	93	>99 / 1	92
16[c, e, g]	2f	C (10)	Bu	90	91 / 9	85
17[b, h]	R3SnO 2g	B (10)	Me	95	92 / 8	82
18[d, f, h]	OSnR3 2h	B (10)	Me	92	81 / 19	94

[a] Reactions were conducted with 10 mol % catalyst, 1.0 equiv of nitrosobenzene, and 1.0 equiv of tin enolate in THF at −78 °C for 2 h. [b] *O*-Sn/*C*-Sn = >99/1. [c] *O*-Sn/*C*-Sn = 53/47. [d] *O*-Sn/*C*-Sn = 19/81, *E*/*Z* = 16/84. [e] Reactions were conducted with 10 mol % (*R*)-BINAP·AgOTf, 1.0 equiv of nitrosobenzene, and 2.0 equiv of tin enolate in THF at −78 °C for 2 h. [f] Reactions were conducted with 10 mol % (*R*)-BINAP·AgOTf, 1.0 equiv of nitrosobenzene, and 5.0 equiv of tin enolate in THF at −78 °C for 2 h. [g] Tin enolates were prepared from 1 equiv of acetate and 1 equiv of tin methoxide and distilled. [h] Tin enolates were generated in situ from 1.0 equiv of trichloro acetate and 1.2 equiv of tin methoxide. [i] Catalyst A: (*R*)-BINAP·$AgClO_4$. Catalyst B: (*R*)-TolBINAP·AgOTf. Catalyst C: (*R*)-TolBINAP·$AgClO_4$. [j] Isolated yield of two isomers. [k] Determined by HPLC (Supporting Information).

to the N═O bond catalyzed by Lewis acid. The enantioselective, *O*-selective nitroso aldol process provides direct access to chiral α-hydroxy ketone. Further investigations into the mechanism and catalytic enantioselective variants of this process are currently underway, and results will be reported in due course.



entry	R^1	R^2	conversion	4a / 4d
1	Me	Bu	>99%	22 / 78
2	Bu	Me	>99%	79 / 21



catalyst	conditions	yield,%	ee, %
none	0 °C, 36 h	63	96
$CuSO_4$ (0.3 eq)	0 °C, 12 h	93	97

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Supporting Information Available: Representative experimental procedure and spectral data for **3a**−**h** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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