Thieme Chemistry Journal Awardees – Where are They Now? Dibutyltin Dimethoxide Catalyzed *N*-Nitrosoaldol Reaction of Alkenyl Trichloroacetate

Akira Yanagisawa,*[a] Youhei Izumi,[b] Satoshi Takeshita[a]

[a] Department of Chemistry, Graduate School of Science, Chiba University, Inage, Chiba 263-8522, Japan
Fax +81(43)2902789; E-mail: ayanagi@faculty.chiba-u.jp

[b] Graduate School of Science and Technology, Chiba University, Inage, Chiba 263-8522, Japan

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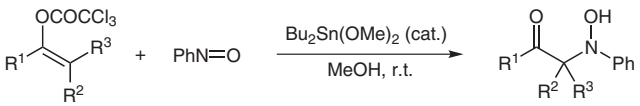
Abstract: Nitrosoaldol reaction between alkenyl trichloroacetates and nitrosobenzene has been achieved using dibutyltin dimethoxide as a catalyst, which is regenerated in the presence of methanol. The corresponding α-hydroxyamino ketones (N-adducts) have exclusively formed not only from cyclic alkenyl trichloroacetates but also from acyclic ones.

Key words: tin catalyst, nitrosoaldol reaction, α-hydroxyamino ketone, alkenyl trichloroacetate, nitrosobenzene

Nitrosoaldol reaction is one of the important C–N bond/C–O bond-forming reactions, which provides us with α-hydroxyamino carbonyl compounds and/or α-aminooxy carbonyl compounds.[1–4] In 2002, Momiyama and Yamamoto have reported that organotin enolates undergo addition reaction to nitrosoarenes without any catalyst and yield α-hydroxyamino ketones exclusively.[5] Furthermore, an asymmetric version of this nitrosoaldol reaction has been also achieved by the same group using BINAP·AgX complexes as chiral catalysts.[6] The α-amination reaction of tin enolates is synthetically useful; however, it has a disadvantage that a stoichiometric amount of environmentally less benign organotin compound is essentially required. We have previously shown that aldol reaction of alkenyl trichloroacetates with aldehydes proceeds smoothly under the influence of a catalytic amount of $Bu_2Sn(OMe)_2$ and a stoichiometric amount of MeOH, in which a tin enolate is catalytically generated in situ.[7] We envisioned that if a α-stannyloxy amino ketone, an initial *N*-nitrosoaldol product, is protonated by MeOH and the corresponding tin methoxide is regenerated efficiently, the catalytic nitrosoaldol reaction might be possible to occur. This paper reports a $Bu_2Sn(OMe)_2$-catalyzed *N*-nitrosoaldol reaction of alkenyl trichloroacetates with nitrosobenzene by the assistance of MeOH (Scheme 1).



Scheme 1 The $Bu_2Sn(OMe)_2$-catalyzed *N*-nitrosoaldol reaction

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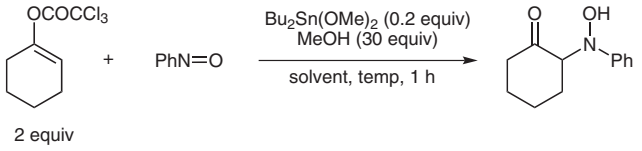
Akira Yanagisawa received his PhD from Nagoya University. He became an Assistant Professor of Nagoya University and an Associate Professor there. In 2001, he moved to Chiba University as a Full Professor. His research interests focus on the development of new synthetic methods using allylic organometallics such as allylic barium reagents and asymmetric synthesis including BINAP·silver(I)-catalyzed asymmetric carbon–carbon bond-forming reactions and asymmetric protonations of metal enolates.

First of all, we attempted a reaction between 1-trichloroacetoxycyclohexene (2 equiv) and nitrosobenzene (1 equiv) in the presence of $Bu_2Sn(OMe)_2$ (0.2 equiv) and MeOH (30 equiv) in THF at room temperature for one hour. As a result, the corresponding α-hydroxyamino ketone (N-adduct) was obtained in 76% yield without formation of any byproducts including its dehydrated product and an alternative α-aminooxy ketone (O-adduct) as shown in entry 1 of Table 1. In order to gain more satisfactory results, we then performed optimization of the reaction conditions. Among the solvents tested, toluene was found to give a higher yield under the similar reaction conditions (entry 3). However, to our great surprise, MeOH was the most effective solvent and indeed the desired product was formed almost quantitatively notwithstanding the possibility of protonation of an in situ generating tin enolate with a large excess amount of MeOH (entry 5). We further tested temperature effect on the chemical yield of the reaction in MeOH and as a consequence, both lower and higher temperatures caused decrease in the yield (entries 6 and 7).

Then, we investigated catalytic activity of several organotin(IV) compounds besides $Bu_2Sn(OMe)_2$ under the optimized reaction conditions (Table 2). Employment of organotin methoxides instead of the organotin dimethoxide decreased the chemical yield (entries 2 and 3). Al-

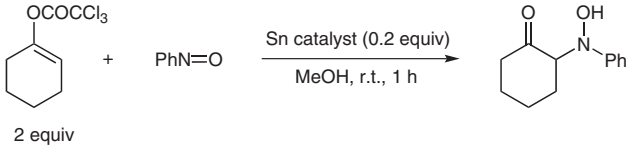
Table 1 Solvent and Temperature Effects on Nitrosoaldol Reaction of an Alkenyl Trichloroacetate of Cyclohexanone with Nitrosobenzene Catalyzed by $Bu_2Sn(OMe)_2$[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]
1	THF	r.t.	76
2	DMF	r.t.	55
3	toluene	r.t.	86
4	CH_2Cl_2	r.t.	52
5	MeOH	r.t.	98
6	MeOH	0	92
7	MeOH	40	79

[a] The reaction was performed using alkenyl trichloroacetate (2 equiv), nitrosobenzene (1 equiv), $Bu_2Sn(OMe)_2$ (0.2 equiv), and MeOH (30 equiv) in a specified solvent at r.t. (entries 1–5), 0 °C (entry 6), or 40 °C (entry 7) for 1 h.
[b] Isolated yield.

Table 2 Screening of Tin Catalysts in Nitrosoaldol Reaction of 1-Trichloroacetoxy Cyclohexene with Nitrosobenzene[a]



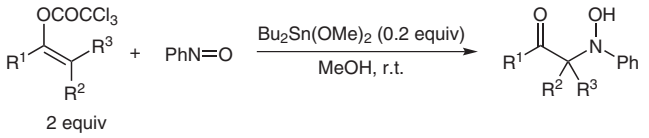
Entry	Tin catalyst	Yield (%)[b]
1	$Bu_2Sn(OMe)_2$	98
2	Bu_3SnOMe	41
3	Me_3SnOMe[c]	20
4	Bu_2SnO	55

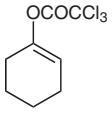
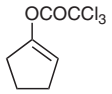
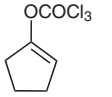
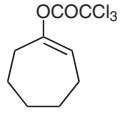
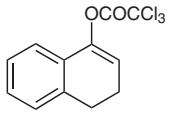
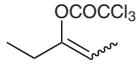
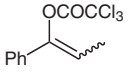
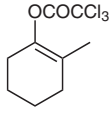
[a] The reaction was carried out employing alkenyl trichloroacetate (2 equiv), nitrosobenzene (1 equiv), and tin catalyst (0.2 equiv) in MeOH at r.t. for 1 h.
[b] Isolated yield.
[c] Prepared from Me_3SnNMe_2 and MeOH.

though dibutyltin oxide also indicated moderate activity in the present nitrosoaldol reaction (entry 4), as a result, $Bu_2Sn(OMe)_2$ was found to be a catalyst of choice (entry 1).

With the most promising tin catalyst at hand, we finally carried out the α-amination of various ketone-derived alkenyl trichloroacetates with nitrosobenzene. The results are summarized in Table 3. This catalytic reaction can be applied not only to cyclic alkenyl esters but also to acyclic ones and the corresponding α-hydroxyamino ketones were obtained in high yield except for a cyclopentanone derivative which afforded a low yield due to rapid protonation of in situ generating tin enolate with MeOH (entry 2). However, the protonation was suppressed to a certain extent when the reaction was performed in toluene as a solvent (entry 3). In every case, no α-aminooxy ketone was contaminated. In addition, other side reactions such as double α-hydroxyamination were not observed at all, which means that the reaction conditions are almost neutral. Noteworthy was the fact that even a fully substituted alkenyl trichloroacetate gave a targeted product in a nearly quantitative yield (entry 8).

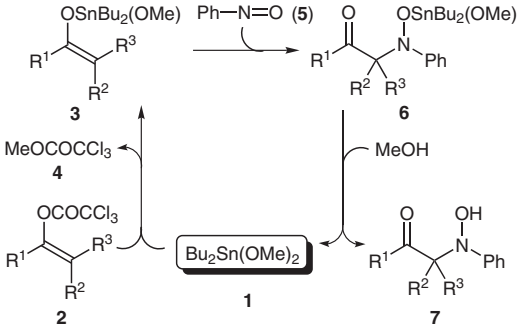
Table 3 $Bu_2Sn(OMe)_2$-Catalyzed Nitrosoaldol Reaction of Various Alkenyl Trichloroacetates with Nitrosobenzene[a]



Entry	Alkenyl trichloroacetate	Time (h)	Yield (%)[b]
1		1	98
2		1	45
3[c]		1	84
4		0.2	98
5		0.2	75
6[d]		1	77
7[d]		0.2	88
8		1	99

[a] The reaction was carried out using alkenyl trichloroacetate (2 equiv), nitrosobenzene (1 equiv), and $Bu_2Sn(OMe)_2$ (0.2 equiv) in MeOH at r.t.
[b] Isolated yield.
[c] The reaction was performed in toluene in the presence of MeOH (30 equiv).
[d] A 1:4 mixture of *E*- and *Z*-isomers were used.

A probable catalytic mechanism for the present nitrosoaldol reaction is shown in Scheme 2. Initially,



Scheme 2 A plausible catalytic cycle

$Bu_2Sn(OMe)_2$ (**1**) reacts with alkenyl trichloroacetate **2** to give tin enolate **3** and methyl trichloroacetate (**4**). Then the resulting tin enolate **3** is allowed to add to nitrosobenzene (**5**), furnishing a tin alkoxide of α-hydroxyamino ketone **6**. Finally, methanolysis of the tin alkoxide **6** completes the catalytic cycle by regenerating the tin dimethoxide **1** accompanied with the desired product **7**.

In summary, we have achieved a $Bu_2Sn(OMe)_2$-catalyzed nitrosoaldol reaction. The tin catalyst is effectively regenerated under the influence of methanol and various α-hydroxyamino ketones can be obtained in satisfactory yield. The procedure is operationally simple and can be performed using readily available chemicals under almost neutral conditions.

Typical Experimental Procedure for the Nitrosoaldol Reaction – Synthesis of 2-(*N*-Phenylhydroxyamino)cyclohexanone (Entry 1, Table 3)[6b]

1-Trichloroacetoxycyclohexene (1.0 mmol) and nitrosobenzene (0.50 mmol) were dissolved in anhyd MeOH (3 mL) under argon atmosphere, and then dibutyltin dimethoxide (0.10 mmol) was added to the resulting solution at r.t. After being stirred for 1 h at this temperature, the mixture was treated with solid KF (ca. 1 g) and brine (1 mL) at ambient temperature for 10 min. After separation of the layers, the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on SiO_2 (neutral) to give 2-(*N*-phenylhydroxyamino)cyclohexanone (0.49 mmol, 98% yield).

TLC: R_f = 0.20 (hexane–EtOAc, 5:1). IR (neat): 3475, 2956, 2862, 1712, 1599, 1487, 1398 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.75 (m, 2 H, CH_2), 1.93–2.02 (m, 1 H, one proton of CH_2), 2.05–2.16 (m, 3 H, CH_2 and one proton of CH_2), 2.35–2.45 (m, 1 H, one proton of CH_2), 2.51–2.58 (m, 1 H, one proton of CH_2), 4.24 (dd, 1 H, *J* = 10.4, 7.5 Hz, CH), 6.18 (s, 1 H, OH), 6.95 (t, 1 H, *J* = 7.4 Hz, arom.), 7.06 (d, 2 H, *J* = 7.7 Hz, arom.), 7.28 (t, 2 H, *J* = 7.4 Hz, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 27.3, 28.0, 42.1, 72.5, 116.0 (2 C), 121.7, 128.7 (2 C), 150.2, 209.7. The above-mentioned spectral data indicated good agreement with reported data.[6b]

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