Highly Diastereoselective Aldol Synthesis from α-Iodo Ketones in Aqueous Media

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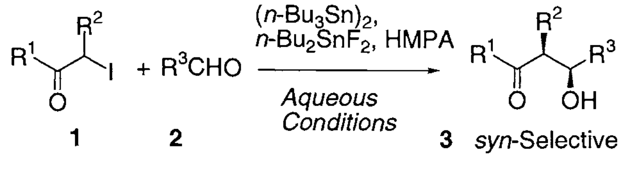
Highly diastereoselective aldol synthesis from α-iodo ketones was promoted under aqueous conditions by a distannane system, $(n\text{-}Bu_3Sn)_2$, $n\text{-}Bu_2SnF_2$ and HMPA. Aqueous solutions of acetaldehyde, formaldehyde and pivaraldehyde were applicable to give β-hydroxy ketones effectively.

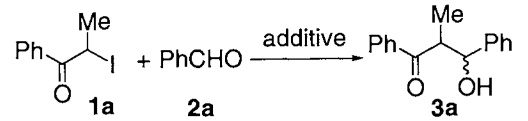
Recently, a carbon-carbon bond formation in aqueous media is focused because of its convenience.[1-3] The aldol synthesis from α-halo ketones is a versatile method for regioselective carbon-carbon bond formation. To perform the reactions, various organometallic reagents such as EtMgBr,[4] n-BuLi,[4] Et_2Zn,[4] Me_3Al,[4] Et_3B,[4] trialkylstibine,[5] Mn complex,[6] bimetallic systems like Et_2AlCl-Zn[7] and Et_2AlCl-Bu_3SnLi[8] are known. The use of these organometallic reagents has an advantage in terms of equimolar amounts and mild conditions, however, the treatments have been limited under strict anhydrous conditions and diastereoselectivities are remained at a lower level. Although activated metals or metal halides such as Ge,[9] Sn,[10] Co[11] and CeI_3 systems[12] have been applied to the reactions in aprotic solvents with high diastereoselectivities, low diastereoselectivity is a serious problem in aqueous media. For example, Sn metal mediated reaction results in poor selectivities under aqueous conditions[13] in contrast to high selectivities in aprotic solvents.[10] Among various methods so far, indium metal mediated reaction is the only case to afford an efficient diastereoselectivity (*syn* : *anti*= 12:1) under aqueous conditions in the reaction of α-bromopropiophenone with benzaldehyde.[14]

Di-tin compounds, R_3SnSnR_3, are considerably stable toward moisture,[15] and could be a good candidate for the organometal-promoted reaction in aqueous conditions. The low reactivity, however, is a serious problem because the assistance of Pd catalyst has been needed even in anhydrous solvents.[16] We have already reported the aldol synthesis from α-iodo ketones by $(n\text{-}Bu_3Sn)_2$ in the presence of $n\text{-}Bu_2SnI_2$-HMPA.[17] In the course of the further studies, we found here that use of $n\text{-}Bu_2SnF_2$, instead of $n\text{-}Bu_2SnI_2$, established a diastereoselective reaction even in aqueous media (Scheme 1). This tin system could induce the example of organometal promoted aldol synthesis in aqueous media. The method gave higher selectivities than in anhydrous media, and could enlarge to use various substrates which are available only as aqueous solutions or include hydroxy groups.



Scheme 1.

Table1. Reformatsky reaction of **1a** and **2a** in aqueous media[a]



Entry	Additive	Solvent	Yield/%[b]	*syn* : *anti*[c]
1	$(n\text{-}Bu_3Sn)_2$	THF/H_2O (3/1)	trace	
2	$(n\text{-}Bu_3Sn)_2$, $n\text{-}Bu_2SnCl_2$	THF/H_2O (3/1)	81	75 : 25
3	$(n\text{-}Bu_3Sn)_2$, $n\text{-}Bu_2SnCl_2$	THF	37	50 : 50
4	$(n\text{-}Bu_3Sn)_2$, $n\text{-}Bu_2SnF_2$	THF/H_2O (3/1)	61	85 : 15
5	$n\text{-}Bu_2SnF_2$	THF/H_2O (3/1)	trace	
6	$(n\text{-}Bu_3Sn)_2$, $n\text{-}Bu_2SnF_2$, HMPA	THF/H_2O (3/1)	80	87 : 13
7	$(n\text{-}Bu_3Sn)_2$, $n\text{-}Bu_2SnF_2$, HMPA	H_2O	75	83 : 17

[a] Iodoketone (**1a**) 1 mmol, Aldehyde (**2a**) 1 mmol, $(n\text{-}Bu_3Sn)_2$ 1 mmol, $n\text{-}Bu_2SnF_2$ 1 mmol, HMPA 1 mmol, THF 1 mL, H_2O 0.35 mL, 60 °C, 3 h. [b] Isolated yield. [c] Determined by ^1H NMR.

Table 1 shows the effects of tin compounds in the reaction of **1a** with **2a** in an aqueous solvent THF/H_2O (3/1). The sole use of $(n\text{-}Bu_3Sn)_2$ gave no desired **3a**, where both **1a** and **2a** were recovered quantitatively (entry 1). When $n\text{-}Bu_2SnCl_2$ was added to the mixture, the yield of **3a** was increased to 81% with 75% *syn*-selectivity (entry 2). This is surprising because the reaction showed no stereoselectivity under aprotic conditions (entry 3). A higher *syn*-selectivity (85%) was obtained by $n\text{-}Bu_2SnF_2$ system (entry 4). Either tin reagent did not effect the reaction at all (entries 1 and 5). The yield and *syn*-selectivity could be raised up to 80% and 87%, respectively, by further addition of HMPA (entry 6). Instead of THF/H_2O, water also gave a similar selectivity (entry 7). This *syn*-selectivity reached the highest level among the reactions so far using various reagents including the reactions under aprotic conditions.

Table 2 shows the facile use of various substrates in an aqueous solvent (THF/H_2O=3/1). The reactions of **1a** with aromatic aldehydes **2b** and **2c** proceeded in good yields with *syn*-selectivities (entries 1 and 2). Enals **2d** and **2e** gave only 1, 2-adducts, **3d** and **3e** (entries 3 and 4). Salicylaldehyde **2f**, which bears hydroxy group, was also reactive to afford **3f** with 90% *syn*-selectivity (entry 5). The reaction of aliphatic aldehyde **2g** gave **3g** in a moderate yield (entry 6). In the cases of **2h**, **2i** and **2j** which are available as aqueous solutions, the reactions proceeded effectively to give **3h**, **3i** and

Table 2. Aldol synthesis in aqueous media[a]

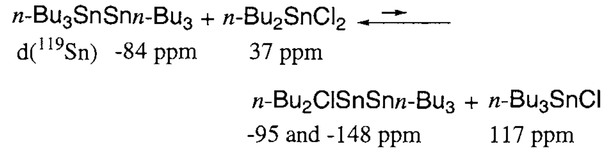
Entry	(1) R^1	(1) R^2	Aldehyde (2)	Product (3)	Yield/%[b] (*syn* : *anti*)[c]
1	Ph	Me(**1a**)	*p*-ClC_6H_4CHO (**2b**)	**3b**	83 (84 : 16)
2			*p*-$NO_2C_6H_4CHO$ (**2c**)	**3c**	90 (80 : 20)
3			(*E*)-PhCH=CHCHO (**2d**)	**3d**	60 (80 : 20)
4			(*E*)-MeCH=CHCHO (**2e**)	**3e**	58 (78 : 22)
5			*o*-HOC_6H_4CHO (**2f**)	**3f**	60 (90 : 10)
6			^{i}PrCHO (**2g**)	**3g**	63[d]
7			CH_3CHO aq. (**2h**)	**3h**	70 (77 : 23)
8			PhCOCHO aq. (**2i**)	**3i**	80 (85 : 15)
9			HCHO aq. (**2j**)	**3j**	70
10	Ph	Ph (**1b**)	**2j**	**3k**	99
11	Ph	H (**1c**)	**2a**	**3l**	55
12	Me	Me(**1d**)	**2a**	**3m**	40 (86 : 14)
13	$(CH_2)_4$ (**1e**)		**2j**	**3n**	55

[a] Iodoketone (**1**) 1 mmol, Aldehyde (**2**) 1 mmol, (*n*-$Bu_3Sn)_2$ 1 mmol, *n*-Bu_2SnF_2 1 mmol, HMPA 1 mmol,THF 1 mL, H_2O 0.35 mL, 60 °C, 3 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Ratio could not be determined.

3j, respectively (entries 7-9). Aromatic ketone **1b** reacted well with **2j** (entry 10). Primary iodo ketone **1c**, alkyl ketones **1d** and **1e** were also applicable (entries 11-13).

We examined the interaction of **1a** with tin reagents used here. When either of (*n*-$Bu_3Sn)_2$ or *n*-Bu_2SnF_2 was treated with **1a** in THF/H_2O at 60 °C for 2 h, no change of **1a** was observed. To the mixture of **1a** and (*n*-$Bu_3Sn)_2$, the addition of Bu_2SnF_2 led to the dehalogenation of **1a** to give propiophenone in 92% yield. Further addition of HMPA increased the yield of propiophenone up to 98%. This tin system did not react with PhCHO at all under same conditions. Namely, the tin system, (*n*-$Bu_3Sn)_2$, *n*-Bu_2SnF_2 and HMPA, seems to react with α-iodo ketones initially.

Although it is still unclear as to the distinct active species, the ^{119}Sn NMR spectra suggested the generation of tin species like *n*-Bu_2XSnSn*n*-Bu_3 (X=halogen) by the redistribution between (*n*-$Bu_3Sn)_2$ and *n*-Bu_2SnCl_2.[18] After heating both tin compounds in THF at 60 °C for 2 h, three new peaks appeared at -95, -148 ppm and 117 ppm. *n*-Bu_3SnCl was confirmed by the peak of 117 ppm. These results suggest the accommodation of the redistribution (Scheme 2).[19]



$$\underset{\text{d}(^{119}\text{Sn})\ \ -84\ \text{ppm}}{n\text{-}Bu_3SnSn\,n\text{-}Bu_3} + \underset{37\ \text{ppm}}{n\text{-}Bu_2SnCl_2} \rightleftharpoons \underset{-95\ \text{and}\ -148\ \text{ppm}}{n\text{-}Bu_2ClSnSn\,n\text{-}Bu_3} + \underset{117\ \text{ppm}}{n\text{-}Bu_3SnCl}$$

Scheme 2.

Although the mechanistic details have not been clear as yet, there is a possibility that *n*-Bu_2FSnSn*n*-Bu_3 reacts with α-iodo ketones to afford the tin enolates which are stable against water. However, tin enolates have not been used in aqueous solvents so far.[20] The higher *syn*-selectivity in aqueous media than the one in aprotic solvent may be explained by the immediate hydrolysis of the Sn-O bond of kinetically formed aldol product. Whereas, under aprotic conditions, the thermodynamic product is formed by an equilibrium of retro-aldol reaction. There is also another possibility that the reaction may proceed through SET mechanism which is already suggested in the indium mediated reaction.[14]

In this way, effective aldol synthesis from α-halo ketones have been performed in good yields with *syn*-selectivities under aqueous conditions. Although present tin system, (*n*-$Bu_3Sn)_2$ and *n*-Bu_2SnF_2, seems to be complex, both tin compounds are easily available and are simply added successively. The use of substrates which are provided as aqueous solutions and contain hydroxy groups is not problem. The investigation of distinct mechanistic studies is now in progress.

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18 The measurement of ^{119}Sn NMR was impossible in the case using *n*-Bu_2SnF_2, because of its low solubility in THF.

19 The fast redistribution could not be incorporated, because a large amount of the starting (*n*-$Bu_3Sn)_2$ (-84 ppm) and *n*-Bu_2SnCl_2 (37 ppm) remained as main signals. Although we also tried to monitor the redistribution in the presence of α-iodo ketone **1a**, the spectrum was complex and we could not obtain any other information as yet.

20 The reaction of organotin enolates is generally performed in only aprotic solvents.[20a,b] In fact, we confirmed that the reaction of easily isolable tri-*n*-butyltin enolate derived from propiophenone with PhCHO at 60 °C for 3 h in THF/H_2O afforded hydrolysis of starting tin enolate, and no desired aldol **3a** was isolated at all. a) M. Pereyre, J. P. Quintard, and A. Rahm, "Tin in Organic Synthesis," Butterworths, London (1987), p. 286. b) I. Shibata and A. Baba, *Org. Prepn and Proc. Int.*, **26**, 85 (1994).