$Sc(OTf)_3$-Catalyzed three-component reactions of aldehydes, amines and allyltributylstannane in micellar systems. Facile synthesis of homoallylic amines in water

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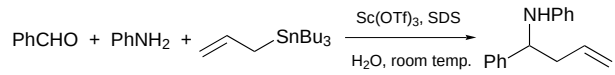
Three-component reactions of aldehydes, amines and allyltributylstannane proceeded smoothly in water without using any organic solvents, in the presence of a small amount of scandium trifluoromethanesulfonate [$Sc(OTf)_3$] and sodium dodecylsulfate (SDS), to afford the corresponding homoallylic amines in high yields.

The reaction of imines with allyltributylstannane provides a useful route for the synthesis of homoallylic amines.[1] The reaction is generally carried out in the presence of a Lewis acid in organic solvents under strict anhydrous conditions,[2] because most imines, Lewis acids and organotin reagents used are hygroscopic and easily decompose in the presence of even a small amount of water.[3] On the other hand, the utility of aqueous reactions is now generally recognized,[4] and development of carbon–carbon bond-forming reactions that can be carried out in aqueous media is one of the most challenging tasks in organic synthesis. It was believed, however, that the above reaction would remain difficult to perform in water because of the use of water-sensitive imines, Lewis acids and organotin reagents. Recently, we have found that scandium trifluoromethanesulfonate [$Sc(OTf)_3$]-catalyzed aldol reactions[5] and allylations of aldehydes[6] proceed smoothly in the presence of a small amount of a surfactant in water. It was indicated that micelles formed in these reactions and that the excellent hydrophobic reaction fields created realized the aqueous reactions. In the course of our investigations to develop new synthetic reactions in micellar systems, we have found that three-component reactions of aldehydes, amines and allyltributylstannane proceed smoothly in micellar systems using $Sc(OTf)_3$ as a Lewis acid catalyst.†

The reaction of benzaldehyde, aniline and allyltributylstannane was chosen as a model, and several sets of reaction conditions were examined. While the reaction proceeded sluggishly in the presence of $Sc(OTf)_3$ without sodium dodecylsulfate (SDS) or in the presence of SDS without $Sc(OTf)_3$, a 77% yield of the desired homoallylic amine was obtained in the presence of both $Sc(OTf)_3$ and SDS. It was suggested that an imine formed from the aldehyde and the amine rapidly reacted with allyltributylstannane to afford the desired adduct. We also examined the effect of the amount of $Sc(OTf)_3$ and SDS used and the results are summarized in Table 1. When a 70 mM SDS solution (0.4 equiv.) was used, the desired homoallylic amine was obtained in a 79% yield, and the yield remained unchanged with increasing amounts of SDS.‡ On the other hand, it was found that reduction of the amount of $Sc(OTf)_3$ decreased the yield, and that a prolonged reaction time increased the yield. Finally, a satisfactory yield was obtained when 0.2 equiv. $Sc(OTf)_3$ and 35 mM (0.2 equiv.) SDS were used and the reaction was carried out at room temp. for 20 h. No homoallylic alcohol (an adduct between the aldehyde and allyltributylstannane) was produced under these conditions.

Several examples of the present three-component reactions of aldehydes, amines and allyltributylstannane are shown in Table 2. The reactions proceeded smoothly in water without using any organic solvents in the presence of a small amount of $Sc(OTf)_3$ and SDS, to afford the corresponding homoallylic amines in high yields. Not only aromatic aldehydes but also aliphatic, unsaturated and heterocyclic aldehydes worked well. It is known that severe side reactions occur to decrease yields in the reactions of imines having α-protons with allyltributylstannane.[1] It should be noted that aliphatic aldehydes, especially non-branched aliphatic aldehydes, reacted smoothly under these conditions to afford the homoallylic amines in high yields. In all cases, no aldehyde adducts (homoallylic alcohols) were ob-

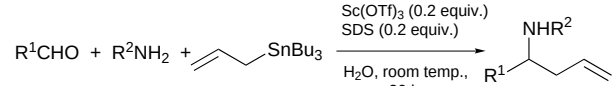
Table 1 Effect of the amounts of $Sc(OTf)_3$ and SDS[a]



$Sc(OTf)_3$/ mol%	SDS/mM	*t*/h	Yield (%)
20	—	4	trace
—	105[b]	4	trace
20	105	4	77
20	18	4	60
20	35	4	68
20	70	4	79
20	140	4	76
10	35	4	52
5	35	4	37
20	35	10	80
20	35	20	83

[a] PhCHO (1.3 equiv.), $PhNH_2$ (1.0 equiv.) and allyltributylstannane (1.5 equiv.). [b] 0.6 equiv.

Table 2 Three-component reactions of aldehydes, amines and allyltributylstannane



R^1	R^2	Yield (%)
Ph	Ph	83
Ph	*p*-ClPh	90
Ph	*p*-MeOPh	81
p-ClPh	*p*-ClPh	70
2-Furyl	*p*-ClPh	67 (71,[a] 82[c])
2-Thienyl	*p*-ClPh	67[a] (78[c])
$Ph(CH_2)_2$	*p*-ClPh	78
$Me(CH_2)_7$	*p*-ClPh	66
c-C_6H_{11}	Ph	80 (83[b])
c-C_6H_{11}	*p*-MeOPh	74
PhCO	*p*-ClPh	71 (83[c])
(*E*)-PhCH=CH	*p*-ClPh	80 (82[a])

[a] SDS, 0.4 equiv. [b] 0.6 equiv. [c] 1.0 equiv.

tained. It was suggested that the imine formation from aldehydes and amines was very fast in the presence of both $Sc(OTf)_3$ and SDS,[8] and that the selective activation of imines rather than aldehydes was achieved using $Sc(OTf)_3$ as a catalyst.[9] It is also noteworthy that using a small amount of a surfactant created efficient hydrophobic reaction fields[10] and achieved the dehydration and addition reactions in water.

A typical experimental procedure is as follows. To a 35 mM water solution of SDS (3 ml) and $Sc(OTf)_3$ (0.1 mmol) were added the amine (0.5 mmol), allyltributylstannane (0.75 mmol) and the aldehyde (0.65 mmol) successively, and the mixture was stirred at room temp. After 20 h, the mixture was diluted with water and ethyl acetate, and Amberlite IRA96SB was added. After being stirred for 10 min, the resin was filtered and the filtrate was extracted with ethyl acetate. The combined organic layers were dried, filtered and concentrated. The crude adduct was purified by column chromatography on silica gel to afford the pure desired homoallylic amine.

In summary, we have developed $Sc(OTf)_3$-catalyzed three-component reactions between aldehydes, amines and allyltributylstannane in micellar systems. The reactions proceed smoothly in water without using any organic solvents, to afford the corresponding homoallylic amines in high yields. In addition to the synthetic utility of these reactions, it should be noted that reactions using water-sensitive substrates have been successfully carried out in water under the present reaction conditions. Further progress is expected in this field and investigations on these micellar systems including mechanistic aspects are now underway in our laboratories.

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Footnotes and References

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† We found that $Sc(OTf)_3$, $Y(OTf)_3$ and $Ln(OTf)_3$ (Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu) are stable Lewis acids in water (ref. 7).

‡ In some other substrates, yields were improved a little with increasing amounts of SDS (see Table 2).

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