Copper(II) Triflate-mediated Addition Reaction of α-Oxygenated Alkylstannanes to Imines for the Synthesis of vicinal-Amino Alcohol Derivatives

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In the presence of copper(II) triflate, a novel addition reaction of α-oxygenated alkylstannanes to various kinds of imines proceeded smoothly to give the corresponding vicinal-amino alcohol derivatives in good yield.

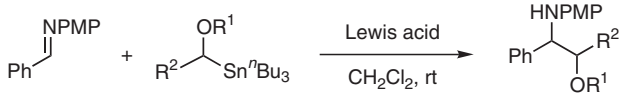
α-Oxygenated allylstannanes are useful reagents for introducing an oxygenated allylic unit upon treatment with electrophiles.[1] For example, Lewis acid-mediated addition reaction of α-oxygenated allylstannanes to aldehydes offers a general route to a variety of vicinal-diol derivatives.[2] Furthermore, the stereochemistry in these reactions has been well studied by using chiral α-oxygenated allylstannanes, and these compounds have been used for the synthesis of optically active vicinal-diol derivatives.[2d,2e] In contrast, little has been known about the synthetic utility of α-oxygenated alkylstannanes as nucleophiles in carbon–carbon bond forming reactions,[3] presumably due to their lower nucleophilicity relative to the corresponding allylstannanes.

As a part of our continuing interest in the development of synthetic methodology using imines,[4] we focused on the reaction of α-oxygenated alkylstannanes with imines leading to vicinal-amino alcohol derivatives.[5] Herein we would like to report the first example of the reaction of α-oxygenated alkylstannanes with imines mediated by $Cu(OTf)_2$, which successfully affords the corresponding vicinal-amino alcohol derivatives in good yield.

At the outset, imine **1a** and α-oxygenated alkylstannanes **2a** were chosen as substrates in the search for optimum conditions, and we examined the effect of Lewis acids in the reaction. The results are summarized in Table 1. When **1a** (1.0 equiv.) and **2a** (1.0 equiv.) were treated with a Lewis acid (1.0 equiv.) such as $BF_3{\cdot}OEt_2$, TMSOTf, $Sn(OTf)_2$, and $SnCl_4$ in CH_2Cl_2, no alkylated product was detected (Entries 1–4). In contrast, use of either $Sc(OTf)_3$ or AgOTf afforded **3a** in moderate yields (Entries 5 and 6). Upon screening various Lewis acids, it was found that yields highly depended on the Lewis acid used and $Cu(OTf)_2$ was the most effective in this reaction (Entry 7). It should be noted that the 1-(methoxymethoxy)butyl group was selectively transferred from the stannane to the imine; no butylated product could be detected in the reaction mixture. In all cases, disappointingly, negligible diastereoselectivity was observed.

Next, the reactions of **1a** with a series of α-oxygenated alkylstannanes **2a–d**[6] were carried out under the influence of $Cu(OTf)_2$ in order to investigate the effect of the substituent on the oxygen atom in the stannanes (Entries 7–10). As a result, it was found that *tert*-butyldimethylsilyl-substituted stannane **2b** reacted more smoothly with **1a** to give **3b** and the yield was comparable to that of **3a** (Entry 8). Use of either acetyl- or methyl-substituted stannanes gave inferior results (Entries 9 and 10). Because variation in the substituent on the oxygen atom revealed that the *tert*-butyldimethylsilyl group was superior with regard to reaction rate and yield, *tert*-butyldimethylsilyl-substituted stannanes were used in further experiments.

Table 1. Effects of Lewis acids and substituents R^1 and R^2 in **2**[a]

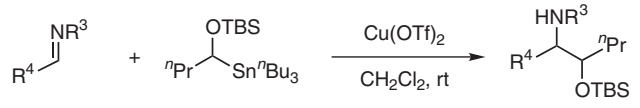


1a **2a-i** **3a-i**

Entry	Lewis acid	**2** R^1	**2** R^2		time/h	**3**	**3** yield/%	**3** *syn*:*anti*[b]
1	$BF_3{\cdot}OEt_2$	MOM	^{n}Pr	**2a**	24	**3a**	0	—
2	TMSOTf	MOM	^{n}Pr	**2a**	24	**3a**	0	—
3	$Sn(OTf)_2$	MOM	^{n}Pr	**2a**	24	**3a**	0	—
4	$SnCl_4$	MOM	^{n}Pr	**2a**	24	**3a**	0	—
5	$Sc(OTf)_3$	MOM	^{n}Pr	**2a**	24	**3a**	48	50:50
6	AgOTf	MOM	^{n}Pr	**2a**	24	**3a**	33	53:47
7	$Cu(OTf)_2$	MOM	^{n}Pr	**2a**	24	**3a**	61	52:48
8	$Cu(OTf)_2$	TBS	^{n}Pr	**2b**	12	**3b**	63	51:49
9	$Cu(OTf)_2$	Ac	^{n}Pr	**2c**	24	**3c**	24	53:47
10	$Cu(OTf)_2$	Me	^{n}Pr	**2d**	24	**3d**	27	48:52
11	$Cu(OTf)_2$	TBS	^{i}Pr	**2e**	12	**3e**	40	51:49
12	$Cu(OTf)_2$	TBS	^{t}Bu	**2f**	12	**3f**	27	70:30
13	$Cu(OTf)_2$	TBS	H	**2g**	12	**3g**	6	—
14	$Cu(OTf)_2$	TBS	Ph	**2h**	6	**3h**	42	55:45
15	$Cu(OTf)_2$	TBS	$TBSO(CH_2)_2$	**2i**	12	**3i**	42	43:57

[a]PMP = 4-methoxyphenyl; MOM = methoxymethyl; TBS = *tert*-butyldimethylsilyl; Ac = acetyl. [b]Determined by 400 MHz ^{1}H NMR.

Table 2. $Cu(OTf)_2$-mediated addition reaction of **2b** to various imines



1a-l **2b** **3b,k-u**

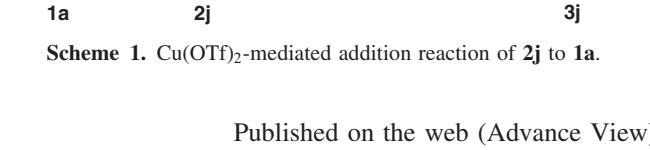
Entry	1			time/h	3		
	R^3	R^4				yield/%	*syn*:*anti*[a]
1	4-$MeOC_6H_4$	Ph	**1a**	12	**3b**	63	51:49
2	4-MeC_6H_4	Ph	**1b**	5	**3k**	74	49:51
3	4-ClC_6H_4	Ph	**1c**	3	**3l**	80	45:55
4	Ph	4-$MeOC_6H_4$	**1d**	3	**3m**	80	50:50
5	Ph	4-MeC_6H_4	**1e**	4	**3n**	68	48:52
6	Ph	4-ClC_6H_4	**1f**	4	**3o**	68	48:52
7	Ph	Ph	**1g**	5	**3p**	59	47:53
8	4-$MeOC_6H_4$	2-furyl	**1h**	7	**3q**	44	51:49
9	4-$MeOC_6H_4$	2-thienyl	**1i**	5	**3r**	37	48:52
10	4-$MeOC_6H_4$	*E*-styryl	**1j**	8	**3s**	58	49:51
11	4-$MeOC_6H_4$	*c*-hexyl	**1k**	18	**3t**	22	51:49
12	4-$MeOC_6H_4$	EtO_2C	**1l**	24	**3u**	82	47:53

[a]Determined by 400 MHz ^{1}H NMR.

Several *tert*-butyldimethylsilyl-substituted stannanes **2e–i**[6] were prepared and employed in the addition reaction with **1a** (Table 1, Entries 11-15). As can be seen from Entries 8, 11, and 12, it is clear that yields of the products were lowered as the alkyl substituent on the α-carbon atom became bulkier. It is noted that moderate *syn* diastereoselectivity was observed when bulky stannane **2f** was used (Entry 12). Not only steric factors but also electronic factors might be important because sterically less demanding **2g** reacted with **1a** to give **3g** in low yield (Entry 13), whereas the reaction of sterically hindered **2j**[6] with **1a** proceeded to afford **3j** in good yield (Scheme 1). We anticipated that α,γ-dioxygenated alkylstannane **2i** would react with **1a** to produce a highly functionalized amino diol derivative. Indeed, the desired product **3i** could be obtained in good yield (Entry 15).

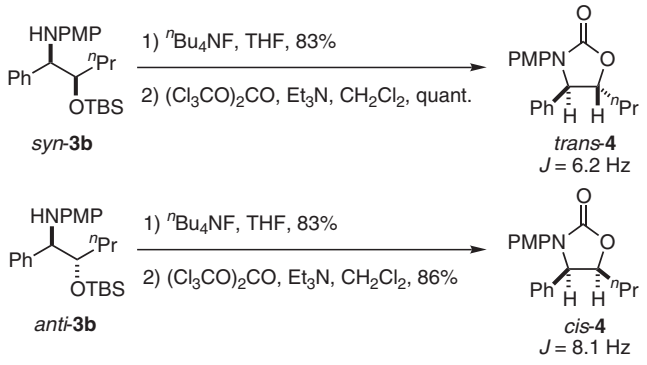
The relative configurations of **3b** were determined by conversion of **3b** into the corresponding oxazolidinones **4** and comparison of their ^{1}H NMR coupling constants with the values of analogous oxazolidinones on the basis of the fact that *cis*-oxazolidinones exhibit larger values than trans-isomers (Scheme 2).[8] For other adducts, the relative configurations were determined by similar derivations and/or on the basis of the ^{1}H NMR analogy with **3b**.

Table 2 summarizes the results of the reactions of various kinds of imines **1a-l** with **2b**.[9] As can be seen from Table 2, imines prepared from aromatic aldehydes and aromatic amines smoothly reacted with **2b** to afford the corresponding vicinal-amino alcohol derivatives in good yields (Entries 1–7). Imines prepared from heteroaromatic aldehydes also furnished the corresponding adducts (Entries 8 and 9). An α,β-unsaturated imine **1j** also worked well. Compared with aromatic- and α,β-unsaturated imines, use of an alkyl-substituted imine **1k** resulted in low yield (Entry 11). Gratifyingly, when an α-imino ester **1l** was used in the reaction with **2b**, the highest yield was achieved (Entry 12). Thus, the present reaction can be applied to the synthesis of α-amino-β-silyloxy esters.



1a **2j** **3j**

Scheme 1. $Cu(OTf)_2$-mediated addition reaction of **2j** to **1a**.



Scheme 2. Determination of the relative configurations of **3b**.

In conclusion, we have developed a copper(II) triflate-mediated addition reaction of α-oxygenated alkylstannanes to imines. The present reaction provides new methodology for the synthesis of vicinal-amino alcohol derivatives. We are currently investigating the scope of this process using other α-heteroatom-substituted alkylstannanes.

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6 These α-oxygenated alkylstannanes were prepared by modifications of the literature procedures for analogous α-oxygenated allyl- and alkylstannanes.[3c,7]

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9 A typical experimental procedure (Table 2, Entry 1): To a mixture of **1a** (21 mg, 0.10 mmol) and $Cu(OTf)_2$ (36 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added **2b** (48 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. After being stirred for 12 h at this temperature, the reaction was quenched with saturated aqueous $NaHCO_3$. After a usual work up, the crude product was purified by TLC (CH_2Cl_2/hexane = 3/4) to give the mixture of diastereomers **3b** (25 mg, 63%, *syn*:*anti* = 51:49).

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