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

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(Received March 10, 2003; CL-030213)

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 BF₃·OEt₂, TMSOTf, Sn(OTf)₂, and SnCl₄ in CH₂Cl₂, 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.

		NPMP OR ¹		Lewis acid $\downarrow B^2$				
		Ph	+ R^2 Sn ⁿ Bu ₃	CH ₂ Cl ₂ ,	rt Ph ²	OR ¹		
		1a	2a-i		38	a-i		
Entry	Lewis acid	2					3	
		\mathbb{R}^1	\mathbb{R}^2		time/h		yield/%	syn:anti ^b
1	$BF_3 \cdot OEt_2$	MOM	ⁿ Pr	2a	24	3a	0	_
2	TMSOTf	MOM	ⁿ Pr	2a	24	3 a	0	_
3	$Sn(OTf)_2$	MOM	ⁿ Pr	2a	24	3 a	0	_
4	SnCl ₄	MOM	ⁿ Pr	2a	24	3 a	0	_
5	Sc(OTf) ₃	MOM	ⁿ Pr	2a	24	3 a	48	50:50
6	AgOTf	MOM	ⁿ Pr	2a	24	3 a	33	53:47
7	Cu(OTf) ₂	MOM	ⁿ Pr	2a	24	3 a	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	Н	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

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

^aPMP = 4-methoxyphenyl; MOM = methoxymethyl; TBS = tert-butyldimethylsilyl; Ac = acetyl. ^bDetermined by 400 MHz ¹H NMR.

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

		OTBS					HNR ³		
i		Ţ	_	Cu(OTI) ₂		4/	/^Pr		
R^4	[^] [^] F	Pr Sn ⁿ Bu ₃		CH ₂ C	l ₂ , rt	Γ R	I OTBS		
1a	a-l	2b				3	3b,k-u		
F (1			3				
Entry	R ³	\mathbb{R}^4		time/h		yield/%	syn:anti ^a		
1	4-MeOC ₆ H ₄	Ph	1a	12	3b	63	51:49		
2	4-MeC ₆ H ₄	Ph	1b	5	3k	74	49:51		
3	$4-ClC_6H_4$	Ph	1c	3	31	80	45:55		
4	Ph	4-MeOC ₆ H ₄	1d	3	3m	80	50:50		
5	Ph	4-MeC ₆ H ₄	1e	4	3n	68	48:52		
6	Ph	$4-ClC_6H_4$	1f	4	30	68	48:52		
7	Ph	Ph	1g	5	3p	59	47:53		
8	4-MeOC ₆ H ₄	2-furyl	1h	7	3q	44	51:49		
9	4-MeOC ₆ H ₄	2-thienyl	1i	5	3r	37	48:52		
10	4-MeOC ₆ H ₄	E-styryl	1j	8	3s	58	49:51		
11	4-MeOC ₆ H ₄	c-hexyl	1k	18	3t	22	51:49		
12	4-MeOC ₆ H ₄	EtO ₂ C	11	24	3u	82	47:53		

^aDetermined by 400 MHz ¹H 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 ¹H 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 ¹H 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 vicinalamino 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



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



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

low yield (Entry 11). Gratifyingly, when an α -imino ester **11** 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.

In conclusion, we have developed a copper(II) triflatemediated 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.

This work was partially supported by the Grant-in-Aid for Young Scientists (B) from Japan Society for the Promotion of Science, the Pfizer Pharmaceuticals Award in Synthetic Organic Chemistry, Japan, and the Mitsubishi Chemical Corporation Fund.

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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 CH₂Cl₂ (1 mL) was added 2b (48 mg, 0.10 mmol) in CH₂Cl₂ (0.5 mL) at room temperature. After being stirred for 12h at this temperature, the reaction was quenched with saturated aqueous NaHCO₃. After a usual work up, the crude product was purified by TLC (CH₂Cl₂/hexane = 3/4) to give the mixture of diastereomers 3b (25 mg, 63%, syn:anti = 51:49).

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Published on the web (Advance View) May 13, 2003; DOI 10.1246/cl.2003.514