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Synthesis of Morita-Baylis-Hillman-type adducts by unprecedented reaction of 1-phenyl-2-(trimethylsilyl)acetylene with aromatic aldehydes catalyzed by quaternary ammonium fluorides derived from cinchonine

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Abstract—The quaternary ammonium fluoride derived from cinchonine efficiently catalyzed the reaction of 1-phenyl-2-(trimethyl-silyl)acetylene with aromatic aldehydes to give the β -branched Morita–Baylis–Hillman-type adducts. © 2005 Elsevier Ltd. All rights reserved.

Quaternary ammonium fluorides derived from cinchona alkaloids have been found to be useful catalysts for the enantioselective carbon–carbon bond forming reactions.^{1,2} However, their applications to organic syntheses are still limited in contrast to tetrabutylammonium fluoride (TBAF), which is widely used as a synthetic reagent for many fluoride-assisted reactions, desilylation, and fluorination as well as a base.³ Thus, the quaternary ammonium fluorides from cinchona alkaloids are expected to be used for a variety of organic reactions.

As an extension of our interests^{1b,d,e} in this topic, we explored the addition reaction of 1-phenyl-2-(trimethylsilyl)acetylene (1) to benzaldehyde (2a) catalyzed by the ammonium fluorides 5 derived from cinchonine, shown in Scheme 1.^{4,5} The major product proved to be not a single addition product 4a but an unexpected β -branched Morita–Baylis–Hillman-type adduct 3a.⁶ We now wish to describe this unprecedented reaction of 1 with aromatic aldehydes 2.⁷

The results from the investigation of the reaction conditions for the reaction of **1** and **2a** are shown in Table 1. The reaction in THF or DMF proceeded at a lower temperature than in CH₂Cl₂ or toluene. In CH₂Cl₂ or toluene, the reaction did not proceed at -20 °C (entries 1– 4). Less than 1 h is sufficient to complete the reaction, and the crude silvlated product was then treated with hydrochloric acid to give the product 3a. The preferred procedure to produce 3a was the addition of the acetylene 1 to a mixture of the catalyst 5a and benzaldehyde (2a). No reaction occurred when the acetylene 1 was first mixed with the catalyst 5a and then the aldehyde 2a was added.⁸ The free hydroxyl group of the catalyst 5a affected the reaction to produce 3a, since its O-allyl and O-benzyl derivatives, 5b and 5c, afforded a mixture of 3a and 4a (compare entries 5-7). The structure of the major product 3a suggested that 2 equiv of the aldehyde 2a would be necessary. However, the use of 1.25-1.50 equiv of the aldehyde 2a will be suitable to save the valuable silvl acetylene 1. Interestingly, the use of less than 1.0 equiv of 2a also gave the Morita-Baylis-Hillman-type adduct 3a as the major product (entries 8-11). To our surprise, the use of TBAF afforded the simple addition product 4a as the major one together with a small amount of 3a.7,9

In all cases, the stereochemistry of the product 3a proved to be the Z-configuration and no signals of the *E*-isomer were observed in the ¹H NMR spectra of the crude product. However, the enantiomeric excess of the product 3a was less than 10% in most cases.

Aldehydes having substituents on the aromatic rings will afford two possible structurally isomeric adducts, **3** and

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Scheme 1.

Table 1. Reaction of the acetylene 1 with benzaldehyde $(2a)^a$

Entry	Catalyst	Solvent	Temp (°C)	2a (equiv)	Yield (%) ^d	
					3a ^e	4a ^f
1	5a	CH_2Cl_2	-20 to rt	1.1	90	_
2	5a	Toluene	-20 to rt	1.1	73	_
3	5a	THF	-20	1.1	73	
4	5a	DMF	-20	1.1	78	_
5 ^b	5a	THF	-20	1.1	80	
6	5b	THF	-20	1.1	49	18
7	5c	THF	-20	1.1	45	27
8	5a	CH_2Cl_2	-20 to rt	0.8	46	9
9	5a	CH_2Cl_2	-20 to rt	1.25	86	2
10	5a	CH_2Cl_2	-20 to rt	1.5	83	2
11	5a	CH_2Cl_2	-20 to rt	2.0	58	4
12 ^b	TBAF ^c	THF	-20	1.1	10	63

 $^{\mathrm{a}}$ To a mixture of the catalyst 5 and benzaldehyde (2a) was added the acetylene 1.

^b To a mixture of the acetylene 1 and benzaldehyde (2a) was added the catalyst 5.

^c THF solution was purchased and used directly.

^d Isolated yield.

^e Yield based on 2a.

^f Yield based on 1.



Table 2.

	ArCHO (2 , 1.5 mmol) 5a (0.1 mmol)		OH	
	1 CH ₂ Cl ₂ N (1.0 mmol) CH ₂ Cl ₂ N -20 to 0 ^o C, 1 h	AeOH O Ar +	4	
Entry	ArCHO	2	Yie	eld (%) ^a
			3 ^b	4 ^c
1	СНО	2a	92	7
2	H ₃ C CHO	2b	87	_
3	МеОсно	2c	37	52
4	FCHO	2d	89	_
5	СІСНО	2e	89	_
6	O ₂ N CHO	2f	_	_
7	MeO MeO CHO	2g	23	26
8	ОСНО	2h	87	_
9	СНО	2i	85	_
10	СНО	2j	54	_
11 ^d	СНО	2k	49 ^e	27

^a Isolated yield.

^b Yield based on ArCHO.

^c Yield based on 1.

^d Phthalaldehyde (0.75 mmol) was used. The crude product was a mixture of stereoisomers (Z:E = 13:87).

^e Product:



6. To clarify the structure of the adduct, 4-fluorobenzaldehyde (2d) reacted with the propargyl alcohols 7a and 7b using tris(triphenylsilyl)vanadate according to the procedure developed by Trost and Oi.¹⁰ The product **6a** obtained from **7a** was not identical to the adduct **3d**, but the major product from **7b** was identical to **3d**, as shown in Scheme 2. Thus the structure of the Morita–Baylis–Hillman-type adduct proved to be **3** and not **6**.



Scheme 3.

Various aldehydes 2 undergo the reaction of 1 to give the Morita-Baylis-Hillman-type adducts 3 having the Z-configuration in moderate to good yields, as summarized in Table 2. 4-Methylbenzaldehyde (2b) smoothly afforded the adduct 3b while 4-methoxybenzaldehyde (2c) afforded a mixture of 3c and 4c in preference of the latter. In contrast, the reaction with *p*-nitrobenzaldehyde (2f) did not proceed at all. Piperonal (2h) proved to be a good substrate for the new reaction, but the reaction with 3,4-dimethoxybenzaldehyde (2g) sluggishly proceeded to give both adducts 3g and 4g in low yields. The major product from phthalaldehyde (2k) was revealed to be the intramolecularly cyclized product 9. Although the E-isomer 9 was mainly obtained in this case, it is considered that the isomerization during the reaction is responsible for the formation of the *E*-isomer.¹¹ Application of aliphatic aldehydes or aliphatic trimethylsilylacetylene to this reaction gave the Morita-Baylis–Hillman-type adducts in trace yields with the simple addition-type products being the major products.

We now propose the mechanism depicted in Scheme 3 for the reaction. The first step involves the addition reaction of the silylacetylene 1 to the aldehyde 2 catalyzed by the fluoride 5a to form the propargylic silyl ether 10. Next, isomerization of the acetylene 10 affords the silyl allenolate 11, followed by the addition of the allenolate toward the second aldehyde 2 at the central carbon of the allenolate.¹² Although no isomerization of 10 was promoted with the quaternary ammonium fluoride 5a at all, treatment of a mixture of 1, 2a, and 10 with the catalyst 5a gave evidence of the conversion of the propargylic silyl ether 10 to the adduct 3a, as shown in Scheme 4.

Thus, the base probably generated in situ is considered to participate in the deprotonation at the propargyl position of 10 and catalyze the isomerization. The Zgeometry preference of the product 3 will be explained by the preferred transition state 12, in which the reaction exclusively occurs from the less hindered site of the allenolate 11. Detailed mechanism about the reaction is still under investigation.



Scheme 4.

In summary, we have developed the unprecedented reaction of 1-phenyl-2-(trimethylsilyl)acetylene (1) with aromatic aldehydes 2 to produce the Z-selective β -branched Morita–Baylis–Hillman-type adducts 3 catalyzed by the quaternary ammonium fluoride 5a derived from cinchonine, and revealed the unusual reactivity of the ammonium fluoride 5a compared with TBAF. The method will be quite useful for the synthesis of β -branched Morita–Baylis–Hillman-type adducts since the β -substituted olefinic substrates do not normally undergo the usual Morita–Baylis–Hillman reaction. A further extension of this reaction is now actively in progress.

The typical procedure for the preparation of the Morita-Baylis-Hillman-type product 3a is as follows: To a solution of the catalyst 5a (40 mg, 0.1 mmol) and benzaldehyde (2a) (0.153 mL, 1.5 mmol) in CH_2Cl_2 (2 mL) was added 1-phenyl-2-(trimethylsilyl)acetylene (1) (0.197 mL, 1.0 mmol) at -20 °C under Ar, then the mixture was immediately warmed to 0 °C. After 1 h, 1 N aq HCl (1 mL) and methanol (4 mL) were added, and the mixture was stirred for only a few minutes. Water, brine, and EtOAc were added, and the separated organic layer was washed with brine and dried over MgSO₄. After removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give the Morita-Baylis-Hillman-type adduct **3a** (219 mg, 92%) and the single addition product **4a** (15 mg, 7%). The spectroscopic data of the main product were indistinguishable from those of 3a reported by Trost and Oi.¹⁰

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