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A convenient method for the synthesis of (*Z*)-α-haloacrylates: Lewis base-catalyzed carbonyl olefination using α-halo-*C*,*O*-bis(trimethylsilyl)ketene acetals

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ABSTRACT

A highly useful method for the stereoselective synthesis of (*Z*)-α-haloacrylates from various aldehydes that uses α-halogenated ethyl-*C*,*O*-bis(trimethylsilyl)ketene acetals in the presence of a Lewis base catalyst such as acetate salts was established. This procedure gives the corresponding α-halo-α,β-unsaturated esters in high yields with excellent stereoselectivity from *E*/*Z* mixtures of ketene silyl acetals under mild conditions.

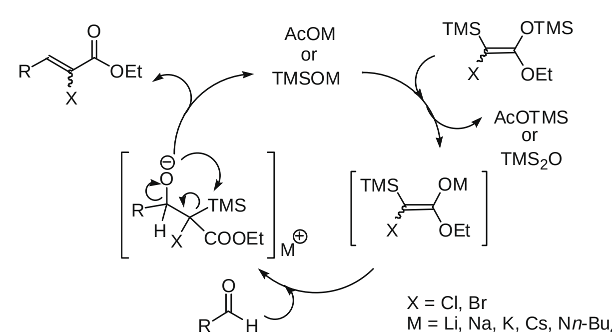
α-Halo-α,β-unsaturated carboxylic esters (α-haloacrylates) are useful building blocks that have haloolefin moiety for synthesizing polymers,[1] or biologically active compounds.[2] Among them, α-chloro and α-bromoacrylates are used frequently for C–C bond forming reactions such as cross coupling reaction[3] or nucleophilic addition[4] in keeping their olefinic geometries. The stereoselective synthesis of α-haloacrylates, therefore, is quite important and versatile for the preparation of various trisubstituted olefins.

Among the synthetic approaches for α-haloacrylates, reactions of aldehydes and α-halophosphonium ylide (Wittig reaction)[5] and α-halophosphonoacetate (Horner–Wadsworth–Emmons reaction)[6] are well known. These reactions are one of the most straightforward methods despite the stereoselectivities that are yet to be solved, and preparations of reagents are often needed to use hazardous or expensive reagents.[7] Recently, Cr(II)-mediated carbonyl olefination by using $CrCl_2$ and trihaloacetate was reported.[8] This reaction is a quite useful method for the stereoselective synthesis of (*Z*)-α-haloacrylates although it requires an excess amount of hazardous metal compounds.

It was shown in our previous report that various acetate salts worked as effective Lewis base catalysts in activating trimethylsilyl (TMS) derivatives in their reactions with electrophiles.[9] More recently, it was also shown that ethyl-*C*,*O*-bis(trimethylsilyl)ketene acetals[10] and α-fluorinated ones[11] are quite useful in the synthesis of α,β-unsaturated esters or (*Z*)-α-fluoroacrylates, which proceeded with high stereoselectivity. Then, α-chloro and α-bromoolefination reactions were examined by using the above combination to expand their utilities. That is, α-haloacrylates are formed directly from aldehydes by the *syn*-elimination of the formed aldol intermediates via the following Lewis base-catalyzed aldol-type reaction (Scheme 1).

In order to investigate carbonyl haloolefination reaction, preparation of reagents **1a** and **1b** was studied. Interestingly, it was found that **1a** and **1b** were directly obtained with the *E*/*Z* = ca 1:1 mixtures from the corresponding inexpensive ethyl haloacetates on treatment with LDA and TMSCl (Scheme 2).[12] It is noted that these olefinating reagents are easily purified by distillation.

Reactions of benzaldehyde **2a** with α-chloro ketene acetal **1a** (*Z*:*E* = 1:1) were tried in the presence of 5 mol % each of various Lewis bases (Table 1). When the reaction was carried out in the presence of AcO*n*-Bu_4N in CH_2Cl_2 that was previously reported as the optimized conditions of this type of reaction, the desired product **3a** was provided in poor yield (entry 1). On the other hand, the yield increased when the reaction was carried out by using various catalysts in DMF (entries 2–6) while its stereoselectivity was poor in the case of AcOLi (entry 2). This result is assumed that the first aldol reaction proceeds via a cyclic (Li-chelated) transition state



Scheme 1. Lewis base-catalyzed carbonyl olefination.

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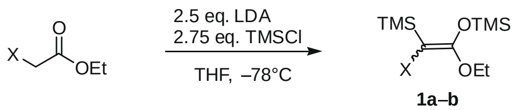
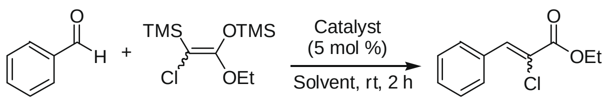


1a–b

1a X = Cl : 50%
1b X = Br : 58%

Scheme 2. Preparation of ketene acetals **1a** and **1b**.

Table 1
Optimization of chloroolefination



2a **1a** (1.2 equiv)[a] **3a**

Entry	Catalyst	Solvent	Yield[b] (%)	Z:E[b]
1	AcO*n*-Bu$_4$N	CH_2Cl_2	37	99:1
2	AcOLi	DMF	83	78:22
3	AcONa	DMF	88	98:2
4	AcOK	DMF	70	99:1
5	AcOCs	DMF	64	97:3
6	AcO*n*-Bu$_4$N	DMF	71	98:2

[a] Ketene acetal **1a** in a ratio of ca 1:1 was used.
[b] Yields and ratios were determined by GC analysis using internal standard.

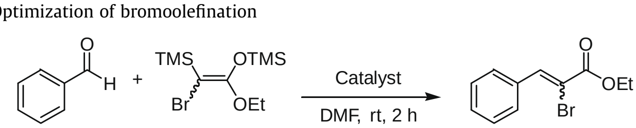
which affords *syn*/*anti* mixture of the aldol intermediate. Consequently, AcONa was the catalyst (entry 3) that gave the best result both in yield and stereoselectivity.[13]

Next, reactions of α-bromo-substituted ketene acetal **1b** (Z:E = 1:1) were studied (Table 2). When the reactions using 5 mol % of various catalysts were carried out, reactions did not complete and a large amount of **2a** and **1a** remained (entries 1–5). In order to complete the reaction, the catalyst loading increased to 10 and 20 mol % (entries 6 and 7). As a result, the reaction proceeded to complete when 20 mol % of AcONa was used and afforded the corresponding (Z)-α-bromoacrylate **4a** in good yield with high stereoselectivity.

Further, reactions of various aldehydes with ketene acetals **1a** and **1b** were tried in the presence of a catalytic amount of AcONa (Table 3). Then, aromatic aldehydes having electron-donating or -withdrawing groups reacted smoothly to afford the corresponding esters **3b**–**e** and **4b**–**e** in good to high yields with high Z-selectivities (entries 1–8). Reactions of heteroarylaldehydes **1f** and **1g** proceeded as well to give **3f**–**g** and **4f**–**g** (entries 9–12).

Thus, a convenient method for the stereoselective synthesis of (Z)-α-haloacrylates by using α-chloro and α-bromo-*C*,*O*-bis(trimethylsilyl)ketene acetals **1a** and **1b** was established. In the presence of a catalytic amount of AcONa, this reaction was observed to proceed smoothly in good to high yield with high Z-selectivity even when E/Z mixture of the ketene acetals was used. In this reaction, TMS_2O that was formed together was removed easily by evaporation. Moreover, these reagents can be prepared in one step from inexpensive ethyl haloacetate. Further studies on this type of reaction are now in progress.

Table 2
Optimization of bromoolefination

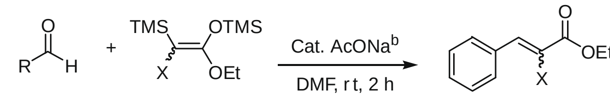


2a **1b** (1.2 equiv)[a] **4a**

Entry	Catalyst (mol %)		Yield[b] (%)	Z:E[b]
1	AcOLi	(5)	30	69:31
2	AcONa	(5)	24	96:4
3	AcOK	(5)	21	97:3
4	AcOCs	(5)	15	94:6
5	AcO*n*-Bu$_4$N	(5)	7	92:8
6	AcONa	(10)	38	96:4
7	AcONa	(20)	75	97:3

[a] Ketene acetal **1b** in a ratio of ca 1:1 was used.
[b] Yields and ratios were determined by GC analysis using internal standard.

Table 3
AcONa-catalyzed carbonyl haloolefination of various aldehydes



2b–g **1a**, **1b** (1.2 equiv)[a] **3b–g**, **4b–g**

Entry	Aldehyde	2	X	Product	Yield[c] (%)	Z:E[b]
1	2-ClC_6H_4	**b**	Cl	**3b**	85	99:1
2	2-ClC_6H_4	**b**	Br	**4b**	77	99:1
3	4-ClC_6H_4	**c**	Cl	**3c**	76	99:1
4	4-ClC_6H_4	**c**	Br	**4c**	72	97:3
5	4-$Me_2NC_6H_4$	**d**	Cl	**3d**	92	94:6
6	4-$Me_2NC_6H_4$	**d**	Br	**4d**	67	92:8
7	4-$MeO_2CC_6H_4$	**e**	Cl	**3e**	81	98:2
8	4-$MeO_2CC_6H_4$	**e**	Br	**4e**	58	98:2
9	2-Furyl	**f**	Cl	**3f**	93	98:2
10	2-Furyl	**f**	Br	**4f**	79	95:5
11	2-Thiophen	**g**	Cl	**3g**	94	97:3
12	2-Thiophen	**g**	Br	**4g**	74	97:3

[a] Ketene acetals **1a** and**1b** in a ratio of ca 1:1 were used
[b] **1a**: 5 mol % of AcONa, **1b**: 20 mol % of AcONa were used.
[c] Isolated yield.
[d] Diastereomeric ratios were determined by GC analysis.

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12. *Preparation* of **1a**: To a mixture of ethyl chloroacetate (103.7 mmol) and TMSCl (285.2 mmol) in THF (40 mL) at −78 °C was added dropwise a THF solution (60 mL) of lithium diisopropylamide prepared by reaction of diisopropylamine (259.3 mmol) with *n*-BuLi (2.6 M in hexane, 259.3 mmol). The resulting mixture was stirred for 2 h and gradually raised to room temperature. To the reaction mixture was added dry hexane (200 mL) and filtered. The filtrate was evaporated, which was distilled to afford the desired product as clear liquid (50% isolated yield, E/Z = 1:1).
13. To a stirred solution of aldehyde (0.5 mmol) and AcONa (0.025 mmol) in DMF (2.5 mL) was added dropwise ketene acetal **1a** (0.6 mmol) at room temperature and stirred for 2 h. The reaction mixture was quenched by aqueous 1 M HCl (0.5 mL) and extracted with brine (5 mL) and AcOEt (15 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by preparative TLC to give the desired product.