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# A New Halo Aldol Reaction: Three-Component Reaction via 1,4-Robust Activation of Ethynyl Alkyl Ketones for Stereoselective Formations of Versatile Aldol Adducts

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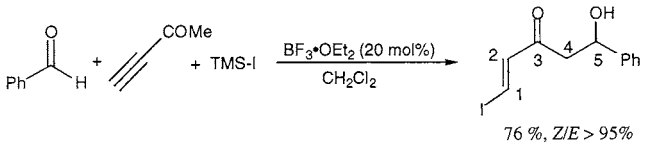
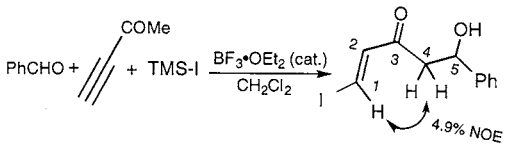
## ABSTRACT




**A new three-component halo aldol reaction has been discovered for the tandem formations of I–C/C–C bonds by activating the α′,β-positions of α,β-acetylenic ketones. The key intermediates, 1-iodo-3-siloxy-1,3-butadienes, were generated from allenolates and directly monitored by $^1$H NMR spectroscopic analysis. Excellent geometric selectivity (>95%) and good yields (65–82%) have been achieved for 10 examples.**

The discovery of new reactions, particularly those involving multiple components in regio- and stereoselective fashions, has been a challenging topic in modern organic chemistry.[1,2] The aldol reaction including reductive and halogeno aldol processes has attracted widespread interest and has been serving as one of the most important tools for organic synthesis.[3−7] In this communication, we report a new organic reaction via a tandem functionalization of 1,4-positions of ethynyl alkyl ketones (Scheme 1). The new three-component reaction proceeds through the α,β-conjugate addition of TMS−I onto ethynyl alkyl ketones followed by unprec-

**Scheme 1**

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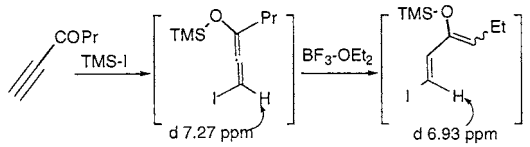
edented catalytic isomerization and aldol reaction in a one-pot operation. The products generated from this new reaction are extremely useful for total synthesis of many biologically important targets such as brevetoxin, kurzilactone, phorboxazole A, mycalolide A, and swinholide A.[8−12] The Danishefsky-type diene intermediates from the catalytic activation of allenolates (Scheme 2) are extremely important

**Scheme 2**




not only for the present carbon−carbon bond formation but also for the Diels−Alder and related reactions.[12]

The new catalytic process was monitored by carefully carrying out the reaction in an NMR tube with ethynyl propyl ketone as the substrate (Scheme 2). A mixture of $\beta$-iodo TMS-allenolate and diene intermediate was directly detected. In their $^1$H NMR spectra, the terminal proton of $\beta$-iodo TMS-allenolate appears at $\delta$ 7.27 ppm as a triplet ($J$ = 9.45 Hz). After conversion into a silyloxydiene intermediate, this proton is slightly shifted upfield to $\delta$ 6.93 ppm as a doublet ($J$ = 17.90 Hz), whereas the corresponding proton of the minor diene intermediate was shifted downfield to $\delta$ 7.92 ppm with a coupling constant of 18.77 Hz. In this particular case, two isomeric products were obtained after the aldol reaction in a ratio of 2.0/1.0 (syn/anti). Unfortunately, these two isomers cannot be separated via column chromatography. To make the initial study simple, ethynyl methyl ketone was chosen as the substrate that could avoid the syn/anti stereoselective problem. Fortunately, in all of the cases we examined, (*E*)-geometry was completely controlled as revealed by crude $^1$H NMR analysis, which enabled us to obtain pure aldol products for full characterizations. The (*E*)-geometry was determined by a NOE experiment on the product in which 4.9% enhancement was observed between the signals of the vinyl proton (position 1) and methylene protons (position 4) as indicated in Scheme 1.

This new process was initiated by our ongoing project on the asymmetric catalytic C(sp$^3$)−C(sp$^2$) bond formation, which serves as the first asymmetric aldol reaction of allenolates with aldehydes (Scheme 3).[13] The reaction was achieved by using *N*-$C_3F_7CO$ oxazaborolidine as the catalyst where the perfluoroacyl group was found to be crucial for

**Scheme 3**

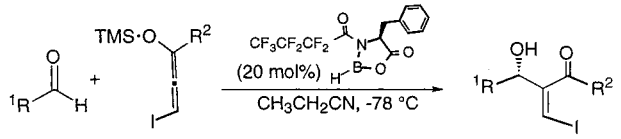
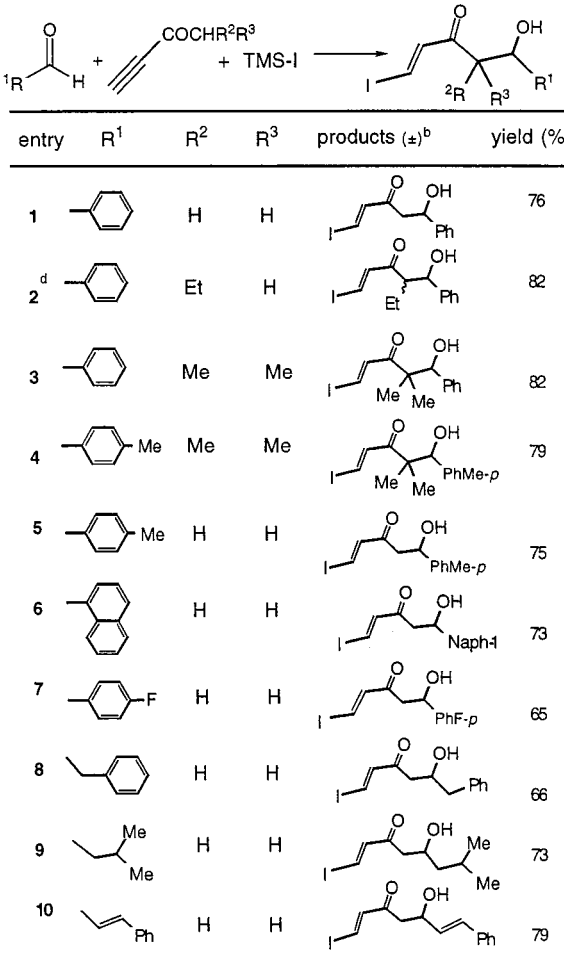



**Table 1.** Results of the Three-Component Reaction[a]




[a] Typical procedure. Into a flame dried flask was dissolved ethynyl methyl ketone (0.10 mL, 1.3 mmol) in dichloromethane (1.5 mL) and cooled to −78 °C followed by dropwise addition of trimethylsilyl iodide (0.18 mL, 1.2 mmol) over 2 min. The resulting mixture was stirrred at −78 °C for 20 min and then at 0 °C for 1 h to afford $\beta$-iodo TMS-allenolate. The mixture was then cooled to −15 °C before one-pot addition of $BF_3$−$OEt_2$ (20 mol %) and benzaldehyde (107 mg, 1.0 mmol). The reaction was stirred at −15 °C for 4 h. It was quenched by dropwise addition of 3 mL of aqueous HCl solution (1 N), and the resulting mixture was stirred at 0 °C for 30 min. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (1/10 v/v EtOAc/hexane) provided a colorless oil product: 229 mg (76% yield). [b] All products appeared as oils. [c] Purified yields after column chromatography. [d] Two isomers (*Z*/*E* = 2:1) were not separable via column chromatography.

the catalytic activity and for the control of enantioselectivity. During that study, a trace amount of side products that were then unknown was found to coexist with $\beta$-halo Baylis−Hillman-type adducts. To make this side reaction the main

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reaction, a variety of commercial Lewis acid catalysts (e.g., $TiCl_4$, $SnCl_4$, $AlCl_3$, $ZnCl_2$, $HgCl_2$, $Cu(OTf)_2$, $FeCl_3$, etc.) were screened. Among the catalysts examined, three of them ($TiCl_4$, $SnCl_4$, and $BF_3-OEt_2$) showed promise, with the last one being the best. In fact, $BF_3-OEt_2$ is the only catalyst that resulted in the desired products without the formation of $\beta$-halo Baylis−Hillman adducts. This catalyst also controlled the (*E*)-geometry completely under the optimized conditions as described in the typical procedure. The catalyst loading of 20 mol % turned out to be necessary for good yields and complete (*E*)-geometry. Decreased loading of catalyst gave complex products as revealed by the crude $^1H$ NMR analysis. During the optimization, several solvents such as $CH_2Cl_2$, $CHCl_3$, MeCN, EtCN, $EtNO_2$, and THF were screened. The first one gave the best results for both yield and *Z*/*E* selectivity. Although the reaction can be performed at −78 °C to give similar results, it needed a much longer reaction period. It is important to note that the low-temperature condition will benefit the asymmetric versions of this reaction.

With $BF_3-OEt_2$ catalyst at hand, we then attempted to use several other analogous allenoates (Cu-, Al-, and Ti-allenoates) for this reaction, but success was very limited. It is surprising that these metal allenolates[7a,14] failed to give any metaloxydiene-derived aldol adducts. A series of combinations of catalysts, solvents, and cosolvents and their ratios will continue to be studied so as to extend the scope of substrates. This situation is similar to our previous catalysis where only $\beta$-iodo TMS-allenolates showed success, while others failed.[13] The in situ generation of $\beta$-iodo TMS-allenolates was carried out by following a known procedure reported by others[15,16] in which TMS−I was added to acetylenic ketones in dichloromethane stirring at low temperature before the $CH_2Cl_2$ solution of $BF_3-OEt_2$ was added. The typical procedure is described by entry 1 of Table 1.

Careful analysis of the preliminary results listed in Table 1 indicates that a good scope of substrates can be employed for this new reaction. Both aromatic (entries 1−7) and aliphatic (entries 8−10) aldehydes can be used as electrophilic acceptors. As anticipated, the reaction of aliphatic aldehydes proceeded at a slightly faster rate than that of aromatic ones to give similar results. Interestingly, the reaction using *trans*-cinnamaldehyde as the electrophile resulted in an extended linear chain consisting of seven carbon atoms with four functional moieties (two C=C bonds, one C=O bond, and one OH group). In regard to Michael-type acceptors for TMS−I, both methyl [−C=O(Me)] and its substituted counterparts [−C=O($CH_2$R)] are effective for this remote activation. The highest yield was obtained with isopropyl ethynyl ketone in which only one proton is available for the activation. A variety of other substituted Michael-type acceptors [HCC−(C=O)$CH_2$X] will be studied to obtain further functionalized aldol products.[17] More importantly, the asymmetric version of this reaction will be investigated in the future.

In summary, a novel multiple-component reaction has been discovered that can provide a concise approach to long-chain aldol adducts. The first catalytic conversion of TMS-allenolates to silyloxydiene intermediates (Danishefsky-type dienes) has been realized and directly observed by direct $^1H$ NMR analysis. Applications of the resulting Danishefsky-type dienes will be studied in due course.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR for pure products. This material is available free of charge via the Internet at http://pubs.acs.org.

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