The stereoselective synthesis of α-amino aldols starting from terminal alkynes.

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A new procedure for the stereoselective synthesis of syn α-amino β-oxy ketones is reported. It consists of two steps; in the first step, α-amino silyl enol ethers having a (Z) geometry are prepared from 1-alkynes via 1-sulfonyl-1,2,3-triazoles. In the second step, the silyl enol ethers undergo the TiCl₄-mediated Mukaiyama aldol reaction with aldehydes to produce α-amino β-oxy ketones with excellent syn-selectivity.

β-Hydroxy carbonyl units are contained in the structures of many natural as well as synthetic target molecules. The directed cross-aldol reaction presents a powerful method for the synthesis of such oxygenated units, and the Mukaiyama aldol reaction using silyl enol ethers (silyl enolates) is one of the most utilized protocols. Silyl enol ethers are usually prepared from the corresponding carbonyl compounds by α-deprotonation using a stoichiometric amount of a base such as lithium diisopropylamide (LDA) and triethylamine. Whereas this carbonyl-based method is useful and practical, an alternative method starting from non-carbonyl precursors would significantly expand the scope of the Mukaiyama aldol chemistry. Furthermore, such methods that would allow the presence of other functional groups are highly desired. We report herein a new sequential procedure starting from 1-alkynes ultimately leading to syn α-amino β-oxy carbonyl compounds, which are substructure often found in various bioactive compounds (Figure 1). The procedure consists of two steps; in the first step, α-amino silyl enol ethers having a (Z) geometry are prepared stereoselectively from 1-alkynes under almost neutral conditions via 1-sulfonyl-1,2,3-triazoles. In the second step, the obtained silyl enol ethers are subjected to the TiCl₄-mediated Mukaiyama aldol reaction with aldehydes to produce syn α-amino β-oxy carbonyl compounds stereoselectively.

Initially, a mixture of phenylethyne (1a, 1.0 equiv), tosyl azide (2a, 1.0 equiv) and copper(I) thiophene-2-carboxylate (10 mol %, CuTC) in chloroform was stirred at room temperature for 6 h to form 4-phenyl-1-tosyl-1,2,3-triazole (3a). Then, tert-butyldimethylsilanol [4 (Si-OH), 1.5 equiv], Rh₂(OCOC₇H₁₅)₄ (1.0 mol %), and 4 Å molecular sieves (4 Å MS) were added to the same reaction vessel, which was heated at 100 °C under microwave irradiation for 15 min. α-Amino silyl enol ether 5a was isolated in 76% yield (eqn (1)). Notably, the (Z)-isomer of 5a was exclusively obtained within the detection limit of ¹H NMR.

Next, the obtained silyl enol ether 5a was treated with 4-chrolobenaldehyde 6a (1.1 equiv) in the presence of TiCl₄ (1.1 equiv)
in dichloromethane at –78 °C for 13 h. An aqueous workup followed by chromatographic isolation afforded α-amino β-siloxy ketone 7aa in 88% yield with excellent syn-selectivity (>95:5). Thus, sequential combination of the two reactions, i.e., the preparation of silyl enol ether and the ensuing Mukaiyama aldol reaction provides a new synthetic pathway starting from 1-alkynes leading to syn α-amino β-oxo ketones.

Scheme 1 presents a mechanistic explanation of this pathway. Initially, a [3+2] cycloaddition reaction of 1a with tosyl azide (2a) occurs at room temperature under the Fokin's conditions. The resulting triazole 3a undergoes a ring-chain tautomerization to generate α-diazo imine 3a', which reacts with rhodium(II) to afford α-imino carbene complex A. Nucleophilic addition of the silanol 4 to the electrophilic carbenoid carbon of A furnishes zwitterionic intermediate B. The anionic rhodium then releases an electron pair, which induces the intramolecular abstraction of the O–H proton by the imine nitrogen to form the (Z)-5a stereoselectively.

In the second step, the Mukaiyama aldol reaction proceeds through the open transition state C, in which the carbonyl oxygen of an aldehyde and the α-amino nitrogen of the silyl enol ether 5a chelate the titanium(IV). The transition state C in which the aryl group of 6a is anti to the α-amino group is favored over the transition state D in which these two groups are gauche, probably due to steric reasons. Thus, the (Z) geometry of 5a is transferred to the syn stereochemistry of the product 7aa.

![Scheme 1](image)

Scheme 1 Plausible mechanism for the formation of syn-7aa.

Other arylethenes 1b–e were subjected to the sequential reaction using the copper(I) and rhodium(II) catalysts to furnish the corresponding (Z)-silyl enol ethers 5b-e in isolated yields ranging from 66% to 76% based on 1a (Table 1, left column). Then, the (Z)-silyl enol ethers 5b-e were reacted with various aldehydes (Table 1, right column). The electron-rich silyl enol ether 5c was more reactive than the electron-deficient one 5d in the Mukaiyama aldol reaction (entries 2 and 3). Of note was that not only aryl aldehydes 6a–d but also alkyl aldehyde 6e exhibited excellent syn-selectivity (>95:5) as well as chemical yield (entry 7).

<table>
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<th>Entry</th>
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</table>

Table 1 Stereoselective Synthesis of α-Amino β-Siloxy Ketones 7 Starting from 1-Alkynes 1a

Other arylethenes 1b–e were subjected to the sequential reaction using the copper(I) and rhodium(II) catalysts to furnish the corresponding (Z)-silyl enol ethers 5b-e in isolated yields ranging from 66% to 76% based on 1 (Table 1, left column). Then, the (Z)-silyl enol ethers 5b-e were reacted with various aldehydes (Table 1, right column). The electron-rich silyl enol ether 5c was more reactive than the electron-deficient one 5d in the Mukaiyama aldol reaction (entries 2 and 3). Of note was that not only aryl aldehydes 6a–d but also alkyl aldehyde 6e exhibited excellent syn-selectivity (>95:5) as well as chemical yield (entry 7).

![Table 2](image)

Table 2 Rh(II)-catalyzed Addition of Silanol 4 to Various 1-Tosyltriazoles 3a

With the sequential procedure in hand, we focused on the reaction of triazoles with silanols in order to delineate its detailed scope. Thus, various isolated 1-tosyl-1,2,3-triazoles 3 were subjected to the reaction with the silanol 4 (Table 2). The 4-aryltriazoles were all competent substrates for the reaction in CHCl3, and the corresponding α-amino silyl enol ethers (5a, 5g–j) were isolated in good to excellent
yields (entries 1–5). The carbonyl groups remained intact, being suggestive of the relatively low basicity of the reaction conditions. A sterically hindered ortho-tolyl group was also eligible as the substituent. On the other hand, modified conditions using 2.5 mol % of Rh2(OCO1-Ad)414 and no solvent were suitable for alkyl-substituted substrates (1g–m), suppressing 1,2-hydride migration potentially occurring with the rhodium carbene complex (entries 6–8). Of particular note was that only (Z)-isomers of 5 were formed within the detection limit of H NMR in all cases.

As for the sulfonyl substituent, not only aryl groups but alkyl groups such as methyl, benzyl and 2-(trimethylsilyl)ethyl groups were all competent (Table 3, entries 1–4). Even a 1,3-dioxan-2-yl substituent, an acid-labile N-protective group, was also suitable (entry 5).

| Table 3 Sulfonyl Substituent of 4-Phenyltriazoles 3^d |
|-----------------|----------------|----------------|
| Entry | 3 | R' | Yield (%) | |
| 1 | 3a | 2-MeO C₆H₄ | 5a | 96 | |
| 2 | 3b | Me | 5b | 85 | |
| 3 | 3p | Ph | 5p | 83 | |
| 4 | 3q | Me₂SCH₂CH₂ | 5q | 91 | |
| 5 | 3r | O | 5r | 92 | |

^a A 0.20 mmol scale. ^b Isolated yield (average of two runs). ^c 120 °C.

For comparison, we attempted to prepare α-amino silyl enol ethers by the conventional preparative method based on α-deprotonation under basic conditions. For example, the α-amino ketone (2-tosylamino-1-phenylethanone) was treated with LDA (2.7 equiv) and subsequently with tert-butyldimethylsilyl chloride (1.7 equiv) at −78 °C. However, only an intractably complex mixture was forming, indicating the poor accessibility of α-amino silyl enol ethers from α-amino ketones. Thus, the present reaction provides an alternative useful preparative method starting from 1-alkynes.

In summary, we have developed a new method for the stereoselective synthesis of syn α-amino β-siloxy ketones starting from 1-alkynes based upon the Mukaiyama aldol reaction of (Z)-α-amino silyl enol ethers, which are difficult to prepare from the corresponding carbonyl compounds.

We thank Dr. Y. Nagata (Kyoto University) for his kind help in an X-ray analysis. This work was supported by MEXT (Grant-in-Aid for Scientific Research on Innovative Areas Nos. 22105005 and 24106718, Young Scientists (A) No. 23685019, Scientific Research (B) No. 23350041) and JST (ACT-C).

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 88th birthday (Beiju).

Notes and references


5. For a reaction of triazoles with PhSiOH, see: S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V. Fokin, J. Am. Chem. Soc., 2014, 136, 195. The resulting triphenylsilyl enol ethers, however, were considerably less reactive than tert-butyldimethylsilyl enol ethers. We attempted the Mukaiyama aldol reaction of triphenylsilyl enol ethers under the identical conditions using TiCl₄ only to recover the starting materials in addition to the corresponding α-amino ketone formed by hydrolysis.

Other silanols such as Me₃SiOH, Et₃SiOH, 'BuPh₂SiOH, and Me₂PhSiOH gave inferior results.

The syn stereochemistry of 7fc was determined by a single-crystal X-ray analysis. Those of other products 7aa and 7ae were determined by NMR. See the supporting information for details.


17 An attempted one-pot sequential reaction of an alkyl-substituted triazole gave a simple hydrolyzed α-amino ketone as the major product with the desired aldol product formed in low yield. The silanol 4 remaining after the first reaction caused hydrolysis of the resulting α-amino silyl enol ether during the subsequent Mukaiyama-aldol reaction.