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Stereoselective Synthesis of α -Amino Aldols Starting from Terminal Alkynes

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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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 TiCl_4 -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)¹ 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 precursors² 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,³ which are substructure often found in various bioactive compounds (Figure 1).⁴ 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

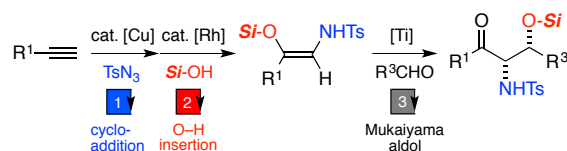
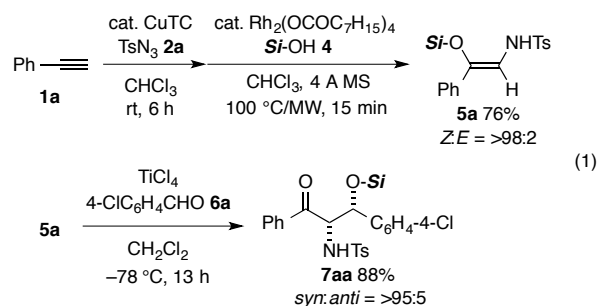


Figure 1 Construction of *syn* α -amino β -siloxy ketones starting from terminal alkynes and tosyl azide.

almost neutral conditions via 1-sulfonyl-1,2,3-triazoles.⁵ In the second step, the obtained silyl enol ethers are subjected to the TiCl_4 -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**).⁶ Then, *tert*-butyldimethylsilylanol [**4** (*Si*-OH), 1.5 equiv],⁷ $\text{Rh}_2(\text{OCOC}_7\text{H}_{15})_4$ (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-chlorobenzaldehyde **6a** (1.1 equiv) in the presence of TiCl_4 (1.1 equiv)



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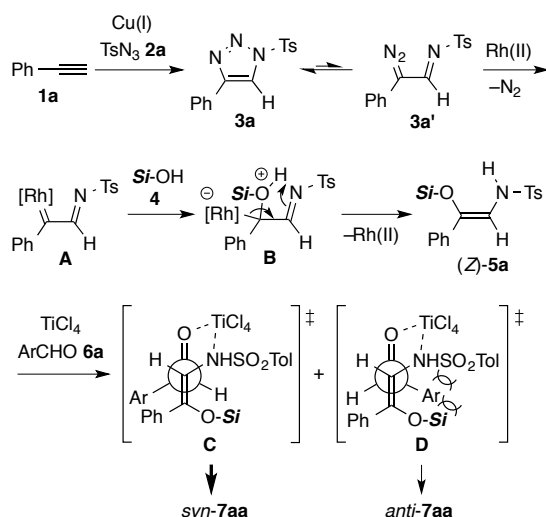
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† Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data for the new compounds and details of the X-ray analysis for compound **7fc**. CCDC 1006110. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c000000x

in dichloromethane at $-78\text{ }^{\circ}\text{C}$ for 13 h. An aqueous workup followed by chromatographic isolation afforded α -amino β -siloxy ketone **7aa** in 88% yield with excellent *syn*-selectivity ($>95:5$).⁸ 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 -oxy 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.⁶ 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**.^{9,20} Nucleophilic addition of the silanol **4** to the electrophilic carbenoid carbon of **A** furnishes zwitterionic intermediate **B**.^{23,22} 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.⁵

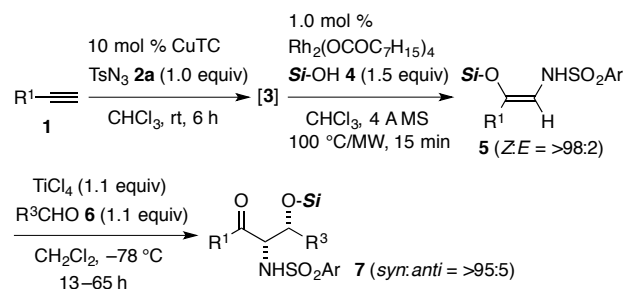
In the second step, the Mukaiyama aldol reaction proceeds through the open transition state **C**, in which the carbonyl oxygen of an aldehyde and the α -amino nitrogen of the silyl enol ether **5a** chelate the titanium(IV).¹³ The transition state **C** in which the aryl group of **6a** is *anti* to 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 Plausible mechanism for the formation of *syn*-**7aa**.

Other aryloalkynes **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 1 Stereoselective Synthesis of α -Amino β -Siloxy Ketones **7** Starting from 1-Alkynes **1**^a



Entry	1 R ¹ -	5 Yield (%) ^{a,b}	6 R ³ -	7 Yield (%) ^{b,c}
1	1b <i>p</i> -Tol-	5b 76	6b Ph-	7bb 80
2	1c <i>p</i> -MeO-C ₆ H ₄ -	5c 66 ^d	6b Ph-	7cb 71
3	1d <i>p</i> -CF ₃ -C ₆ H ₄ -	5d 74 ^e	6a <i>p</i> -Cl-C ₆ H ₄ -	7da 51 ^g
4	1e 3-thienyl-	5e 69	6b Ph-	7eb 79
5	1f Ph- ^f	5f 70	6c <i>p</i> -Br-C ₆ H ₄ -	7fc 75
6	1a Ph-	5a 76	6d <i>p</i> -NO ₂ -C ₆ H ₄ -	7ad 71
7	1a Ph-	5a 76	6e CH ₃ (CH ₂) ₅ -	7ae 91

^a A 0.40 mmol scale. ^b Isolated yield (average of two runs). ^c A 0.20 mmol scale. ^d A small amount of unidentified impurities included. ^e The second step at 120 °C. ^f Using *p*-Br-C₆H₄-SO₂N₃ **2b** (Ar = *p*-Br-C₆H₄-). ^g *syn:anti* = 87:13.

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

Entry	3 R ¹ -	Temp (°C)	5 Yield (%) ^{a,b}
1	3a Ph-	100	5a 96
2	3g <i>p</i> -Ph-C ₆ H ₄ -	100	5g 98
3	3h <i>p</i> -EtO ₂ C-C ₆ H ₄ -	120	5h 85
4	3i <i>p</i> -MeC(O)-C ₆ H ₄ -	120	5i 87
5	3j <i>o</i> -Tol-	140	5j 75 ^c
6	3k ⁿ Pr-	140	5k 71 ^{c,d}
7	3l ⁱ Bu-	140	5l 65 ^{c,d}
8	3m BzO(CH ₂) ₄ -	140	5m 67 ^{c,d}

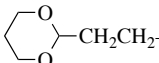
^a A 0.20 mmol scale. ^b Isolated yield (average of two runs). ^c Rh₂(OCOC1-Ad)₄ (2.5 mol %), **4** (6.0 equiv), neat. ^d NMR yield using an internal standard (average of two runs).

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 4-substituent. On the other hand, modified conditions using 2.5 mol % of $\text{Rh}_2(\text{OCO}_1\text{-Ad})_4$ ³⁴ and no solvent were suitable for alkyl-substituted substrates (**3k–m**), suppressing 1,2-hydride migration³⁵ potentially occurring with the rhodium carbene complex (entries 6–8).^{36,37} Of particular note was that only (*Z*)-isomers of **5** were formed within the detection limit of ¹H 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 2-(1,3-dioxan-2-yl)ethyl substituent, an acid-labile *N*-protective group, was also suitable (entry 5).³⁸

Table 3 Sulfonyl Substituent of 4-Phenyltriazoles **3**^a

Entry	3	R ² -	5	Yield (%) ^{a,b}
1	3n	<i>p</i> -MeO-C ₆ H ₄ -	5n	96
2	3o	Me-	5o	85 ^b
3	3p	PhCH ₂ -	5p	82
4	3q	Me ₃ SiCH ₂ CH ₂ -	5q	94
5	3r		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.³⁹ 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.²⁹ However, only an intractably complex mixture was formed, 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).

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