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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 $TiCl_4$-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 precursors[2] 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 substructures often found in various bioactive compounds (Fig. 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 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.

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

‡ 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/c4cc04786a

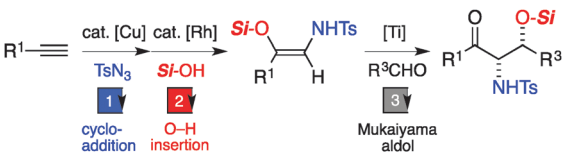
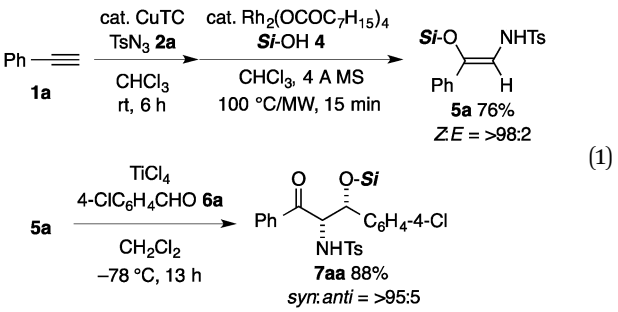


Fig. 1 Construction of *syn* α-amino β-siloxy ketones starting from terminal alkynes and tosyl azide.

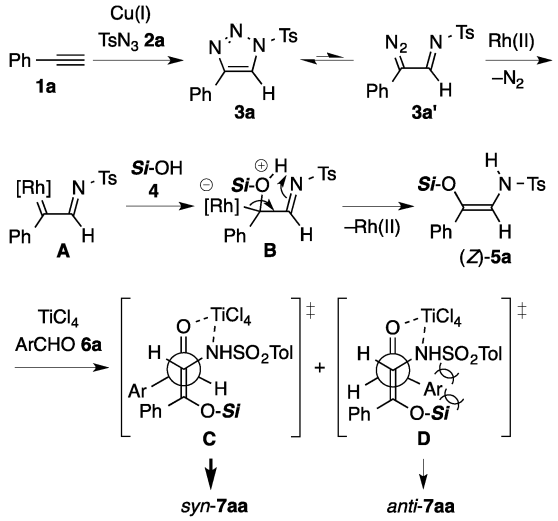
Initially, a mixture of phenylethyne (**1a**, 1.0 equiv.), tosyl azide (**2a**, 1.0 equiv.) and copper(I) thiophene-2-carboxylate (10 mol%, CuTC) in chloroform was stirred at room temperature for 6 h to form 4-phenyl-1-tosyl-1,2,3-triazole (**3a**).[6] Then, *tert*-butyldimethylsilanol [**4** (*Si*-OH), 1.5 equiv.],[7] $Rh_2(OCOC_7H_{15})_4$ (1.0 mol%), and 4 Å molecular sieves (4 A 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 ^{1}H NMR.

Next, the obtained silyl enol ether **5a** was treated with 4-chrolobenzaldehyde **6a** (1.1 equiv.) in the presence of $TiCl_4$ (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).[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.



(1)

Scheme 1 presents a mechanistic explanation for this pathway. Initially, a [3+2] cycloaddition reaction of **1a** with tosyl azide (**2a**)



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

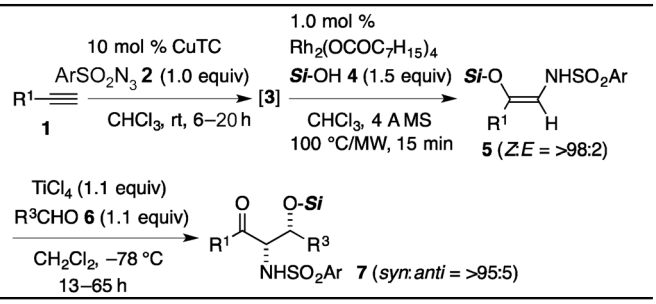
occurs at room temperature under Fokin's conditions.[6] The resulting triazole **3a** undergoes a ring-chain tautomerization to generate α-diazo imine **3a′**, which reacts with rhodium(II) to afford the α-imino carbene complex **A**.[9,10] Nucleophilic addition of the silanol **4** to the electrophilic carbenoid carbon of **A** furnishes the zwitterionic intermediate **B**.[11,12] 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 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**.

Other arylethynes **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).

With the sequential procedure in hand, we focused on the reaction of triazoles with silanols in order to delineate their detailed scope. Thus, various isolated 1-tosyl-1,2,3-triazoles **3** were subjected to the reaction with silanol **4** (Table 2). The 4-aryltriazoles were all competent substrates for the reaction in $CHCl_3$, 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,

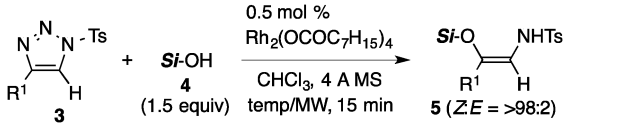
Table 1 Stereoselective synthesis of α-amino β-siloxy ketones **7** starting from 1-alkynes **1**



Entry	1	R^1–	5	Yield[a,b] (%)	6	R^3–	7	Yield[b,c] (%)
1	**1b**	*p*-Tol–	**5b**	76	**6b**	Ph–	**7bb**	80
2	**1c**	*p*-MeO–C_6H_4–	**5c**	66[d]	**6b**	Ph–	**7cb**	71
3	**1d**	*p*-CF_3–C_6H_4–	**5d**	74[e]	**6a**	*p*-Cl–C_6H_4–	**7da**	51[g]
4	**1e**	3-Thienyl–	**5e**	69	**6b**	Ph–	**7eb**	79
5	**1f**	Ph–[f]	**5f**	70	**6c**	*p*-Br–C_6H_4–	**7fc**	75
6	**1a**	Ph–	**5a**	76	**6d**	*p*-NO_2–C_6H_4–	**7ad**	71
7	**1a**	Ph–	**5a**	76	**6e**	$CH_3(CH_2)_5$–	**7ae**	91

[a] A 0.40 mmol scale. Using TsN_3 **2a** (Ar = *p*-Tol-) unless otherwise noted. [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–C_6H_4–SO_2N_3 **2b** (Ar = *p*-Br–C_6H_4–). [g] *Syn* : *anti* = 87 : 13.

Table 2 Rh(II)-catalyzed addition of silanol **4** to various 1-tosyltriazoles **3**



Entry	3	R^1–	Temp (°C)	5	Yield[a,b] (%)
1	**3a**	Ph–	100	**5a**	96
2	**3g**	*p*-Ph–C_6H_4–	100	**5g**	98
3	**3h**	*p*-EtO_2C–C_6H_4–	120	**5h**	85
4	**3i**	*p*-MeC(O)–C_6H_4–	120	**5i**	87
5	**3j**	*o*-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]

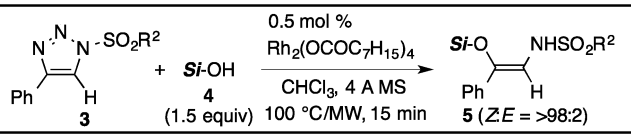
[a] A 0.20 mmol scale. [b] Isolated yield (average of two runs). [c] Rh_2(OCO1-Ad)$_4$ (2.5 mol%), **4** (6.0 equiv.), neat. [d] NMR yield using an internal standard (average of two runs).

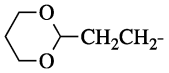
modified conditions using 2.5 mol% of Rh_2(OCO1-Ad)$_4$ (ref. 14) and no solvent were suitable for alkyl-substituted substrates (**3k–m**), suppressing 1,2-hydride migration[15] potentially occurring with the rhodium carbene complex (entries 6–8).[16,17] Of particular note was that only (*Z*)-isomers of **5** were formed within the detection limit of ^{1}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 2-(1,3-dioxan-2-yl)-ethyl substituent, an acid-labile *N*-protective group, was also suitable (entry 5).[18]

For comparison, we attempted to prepare α-amino silyl enol ethers using the conventional preparative method based on α-deprotonation under basic conditions.[19] For example,

Table 3 Sulfonyl substituent of 4-phenyltriazoles **3**



Entry	**3**	R^2–	**5**	Yield[a,b] (%)
1	**3n**	*p*-MeO–C_6H_4–	**5n**	96
2	**3o**	Me–	**5o**	85[c]
3	**3p**	$PhCH_2$–	**5p**	82
4	**3q**	$Me_3SiCH_2CH_2$–	**5q**	94
5	**3r**		**5r**	92

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

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.[20] 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.

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