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EFFICIENT ONE-POT SYNTHESIS OF SUBSTITUTED OXAZOLES FROM 3-TRIMETHYLSILYLPROPARGYLIC ALCOHOLS AND AMIDES BY GOLD-CATALYZED SUBSTITUTION FOLLOWED BY CYCLOISOMERIZATION

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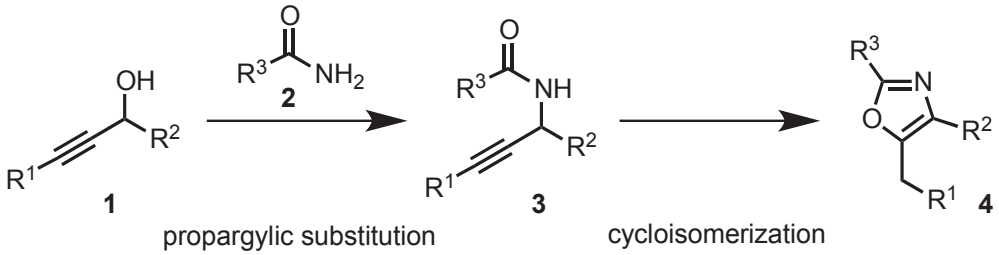
This paper is dedicated to Prof. Dr. Kiyoshi Tomioka on the occasion of his 70th birthday.

Abstract – 3-Trimethylsilylpropargylic alcohols **1**, on treatment with amides **2** in the presence of catalytic amounts of cationic gold(III), underwent propargylic substitution followed by cycloisomerization, in which the key feature is the β-cation-stabilizing effect of the silicon atom of **1**.

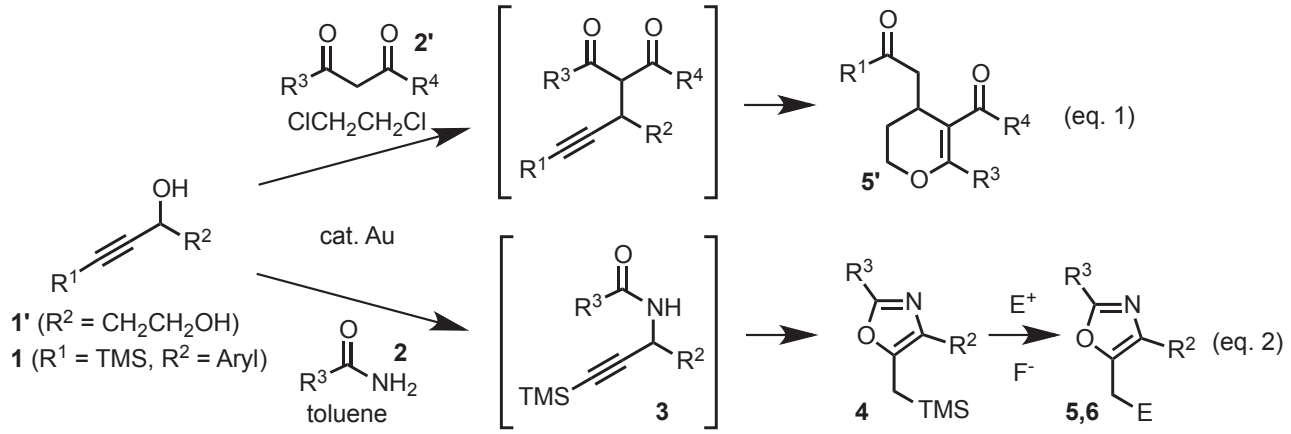
Substituted oxazoles are common substructures in a huge number of natural products and biologically active compounds,[1] as well as in various reagents/intermediates used in organic synthesis.[2] Among the numerous procedures reported for the construction of substituted oxazoles, cycloisomerization of propargylic amides **3** to substituted oxazoles **4** has attracted much attention (Scheme 1).[1] These transformations have employed transition metals[3a] (Pd,[3b,c] Fe,[3d] Au,[3e-k] etc.), as well as other reagents.[4] However, the one-pot synthesis of substituted oxazoles **4** directly from propargylic alcohols **1** and amides **2** via **3** as intermediates remains a challenging task, because both propargylic substitution and the subsequent cycloisomerization should proceed effectively under the same reaction conditions. Recently, efficient syntheses of substituted oxazoles **4** were achieved via propargylic substitution/cycloisomerization of propargylic alcohols **1** and amides **2** using a combination of two different transition metals (Ru/Au,[5] Zn/Ru[6]), but these methods were applicable only to terminal propargylic alcohols **1** (R^1 = H), thus being limited to the formation of oxazoles **4** (R^1 = H) having a methyl group at the 5-position.

Recently, Zhan *et al.* reported a one-pot synthesis of substituted oxazoles **4** from propargylic alcohols **1** and amides **2** with using *p*-toluenesulfonic acid monohydrate (PTSA).[7] Although this procedure has wide scope for the preparation of substituted oxazoles **4** and is superior in that it uses only a single catalyst, a stoichiometric amount of PTSA is needed in the reaction. Thus, more efficient synthetic methods for substituted oxazoles **4** are still required.



Scheme 1

We have developed gold(I)/(III)-catalyzed intramolecular reactions of propargylic alcohols for the synthesis of heterocyclic compounds (cyclic ethers/piperidines/azepanes).[8-10] We also extended this procedure to gold-catalyzed intermolecular reaction of propargylic alcohols with carbon nucleophiles, affording cyclic compounds (indenes/dihydropyrans).[11,12] In particular, we achieved the gold-catalyzed one-pot synthesis of dihydropyrans **5'** from propargylic alcohols **1'** (R^2 = CH_2CH_2OH) with active methylene compounds **2'** via propargylic substitution followed by cyclization (Scheme 2, eq. 1).[12] Based on this result, we envisioned the possible development of a gold-catalyzed one-pot synthetic procedure for substituted oxazoles **4** from propargylic alcohols **1** with amides **2** instead of active methylene compounds **2'** (Scheme 2, eq. 2).

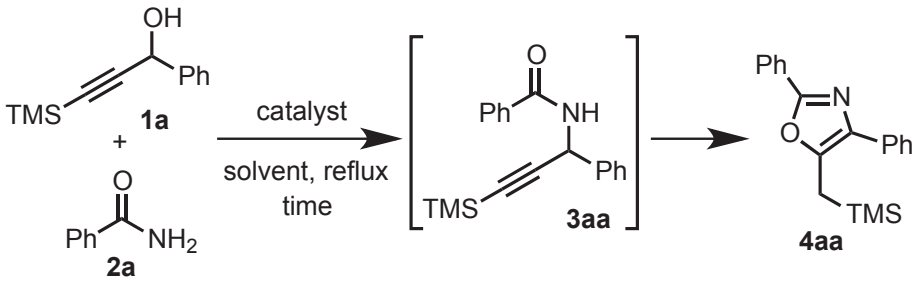


Scheme 2

Herein, we present the one-pot synthesis of substituted oxazoles **4** by gold-catalyzed propargylic substitution followed by cycloisomerization promoted by the β-cation-stabilizing effect[13] of the silicon atom of 3-trimethylsilylpropargylic alcohol **1** (R^1 = TMS). The trimethylsilylmethyl group at the 5-position in the oxazole ring **4** can be easily transformed into other substituents (see **5** and **6**) in the presence of fluoride ion with electrophiles.

We first examined propargylic substitution of 3-trimethylsilylpropargylic alcohol **1a** with benzamide (**2a**) in the presence of an oxophilic gold(III) catalyst that can activate the hydroxyl group at the propargylic position (Table 1). Gold(III) catalyst $AuBr_3$ (5 mol%) afforded a trace amount of the desired oxazole **4aa** (entry 1), whereas cationic gold species generated from $AuBr_3$ (5 mol%) and $AgPF_6$ (15 mol%) gave the desired product **4aa** in 33% yield (entry 2). Next, the effect of the counter anion of silver catalysts was investigated. The reaction with $AuBr_3$ (5 mol%) and AgOTf (15 mol%) gave the desired product **4aa** in good yield (entry 3). In contrast, the reaction with $AuBr_3$ (5 mol%) and $AgBF_4$ (15 mol%) afforded only a trace amount of the product **4aa** (entry 4). The reaction was greatly accelerated in the presence of $AuBr_3$ (5 mol%) and AgOTf (15 mol%) in refluxing toluene, affording oxazole **4aa** in good yield (entry 5). Reducing the catalyst loading to 1 mol% $AuBr_3$ and 3 mol% AgOTf gave 37% yield of **4aa** (entry 6). Finally, the catalyst system of $AuBr_3$ (5 mol%) with AgOTf (15 mol%) in refluxing toluene was identified as optimal for the formation of **4aa**.[14]

Table 1. Optimization of reaction conditions for gold-catalyzed one-pot synthesis of substituted oxzazole **4aa** from 3-trimethylsilylpropargylic alcohol **1a** and benzamide (**2a**)

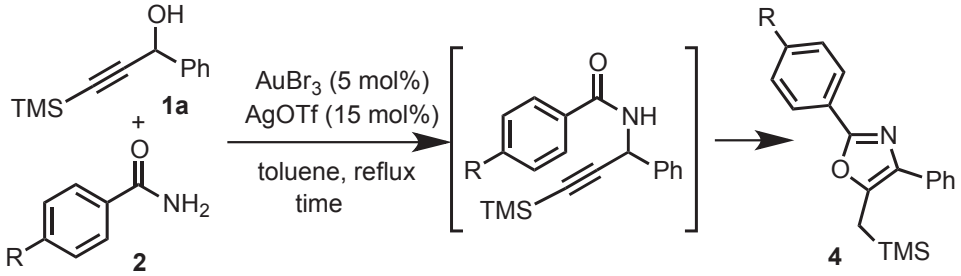


entry	catalyst	solvent	time	**4aa** yield
1	$AuBr_3$ (5 mol%)	$ClCH_2CH_2Cl$	5 days	trace
2	$AuBr_3$ (5 mol%)/$AgPF_6$ (15 mol%)	$ClCH_2CH_2Cl$	2 days	33%
3	$AuBr_3$ (5 mol%)/AgOTf (15 mol%)	$ClCH_2CH_2Cl$	2 days	74%
4	$AuBr_3$ (5 mol%)/$AgBF_4$ (15 mol%)	$ClCH_2CH_2Cl$	2 days	trace
5	$AuBr_3$ (5 mol%)/AgOTf (15 mol%)	toluene	1 h	75%
6	$AuBr_3$ (1 mol%)/AgOTf (3 mol%)	toluene	3 h	37%

We next investigated the gold-catalyzed one-pot synthesis of oxazoles **4** from 3-trimethylsilylpropargylic alcohol **1a** with various 4-substituted benzamides **2** (Table 2). The reaction of **1a** and *p*-tolylamide (**2b**) afforded the corresponding oxazole **4ab** in 66% yield (entry 1). The reaction with *p*-methoxybenzamide (**2c**) also gave the corresponding product **4ac** in similar yield (entry 2), while the reaction with *p*-chlorobenzamide (**2d**) furnished **4ad** in 71% yield (entry 3), but the reaction with *p*-nitrobenzamide (**2e**) afforded **4ae** in only 18% yield (entry 4). There are two possible reasons for the low yield with *p*-nitrobenzamide (**2e**). First, the gold catalyst might be deactivated by coordination of oxygen atom of the nitro group of **2e**. Second, the nucleophilicity of **2e** might be decreased by the electron-withdrawing effect of the nitro group on the aromatic ring.

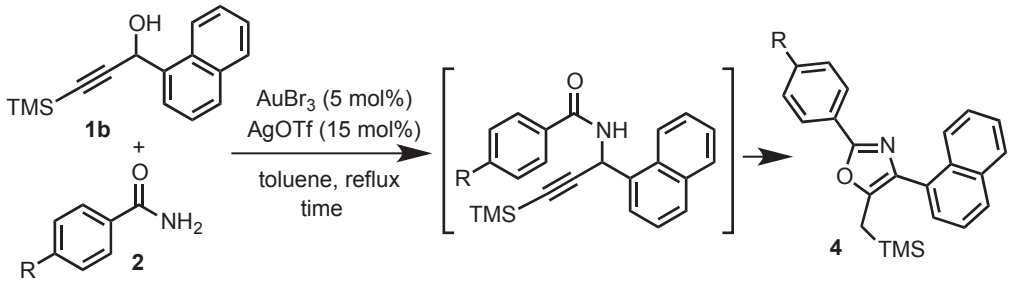
Next, the reaction of 3-trimethylsilylpropargylic alcohol **1b** bearing a naphthyl group at the propargylic position with various amides **2** was examined (Table 3). The reaction of **1b** with *p*-tolylamide (**2b**) gave the corresponding product **4bb** in 74% yield (entry 1), while the reaction with *p*-methoxybenzamide (**2c**) furnished **4bc** in 65% yield (entry 2), and the reaction with *p*-chlorobenzamide (**2d**) afforded the desired product **4bd** in 78% yield (entry 3).

Table 2. The gold-catalyzed one-pot synthesis of substituted oxazoles **4** from propargylic alcohol **1a** with various amides **2**



entry	**2**	time	**4**	yield
1	**2b**: R = Me	7 h	**4ab**	66%
2	**2c**: R = MeO	6 h	**4ac**	66%
3	**2d**: R = Cl	1 h	**4ad**	71%
4	**2e**: R = NO_2	1 h	**4ae**	18%

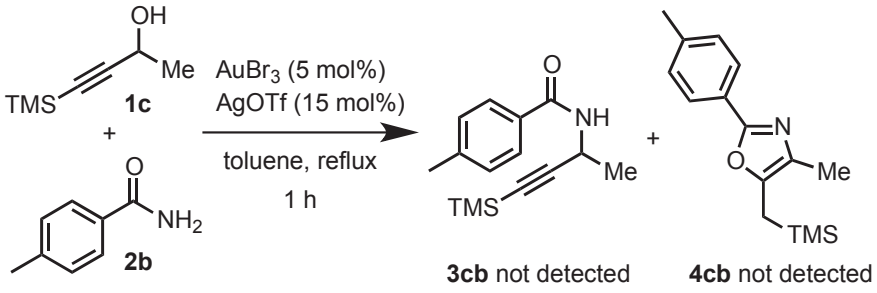
Table 3. The gold-catalyzed one-pot synthesis of substituted oxazoles **4** from propargylic alcohol **1b** with various amides **2**



entry	2	time	4	yield
1	**2b**: R = Me	5 h	**4bb**	74%
2	**2c**: R = MeO	6 h	**4bc**	65%
3	**2d**: R = Cl	4 h	**4bd**	78%

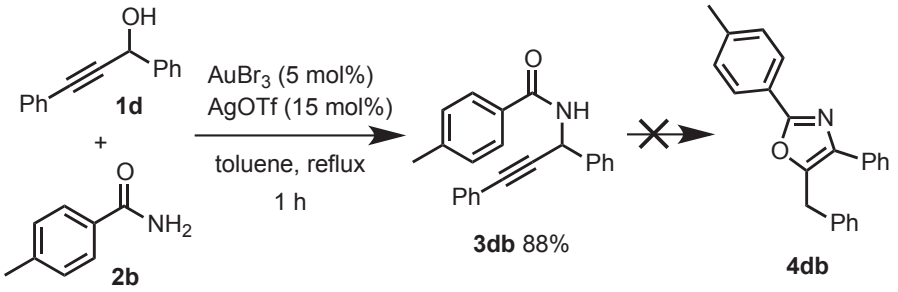
To investigate the scope and limitations of the gold-catalyzed one-pot synthesis of substituted oxazoles **4**, we tried the reaction of propargylic alcohol **1a** with acetamide (**2f**). In the case of acetamide (**2f**), the reaction resulted in a complex mixture (Scheme 3). The reaction of propargylic alcohol **1c** bearing a methyl group at the propargylic position instead of an aryl group afforded neither amide **3cb** nor oxazole **4cb** (Scheme 4), which shows that stabilization of the cation at the propargylic position by the aryl group is important for the propargylic substitution step.

Scheme 3



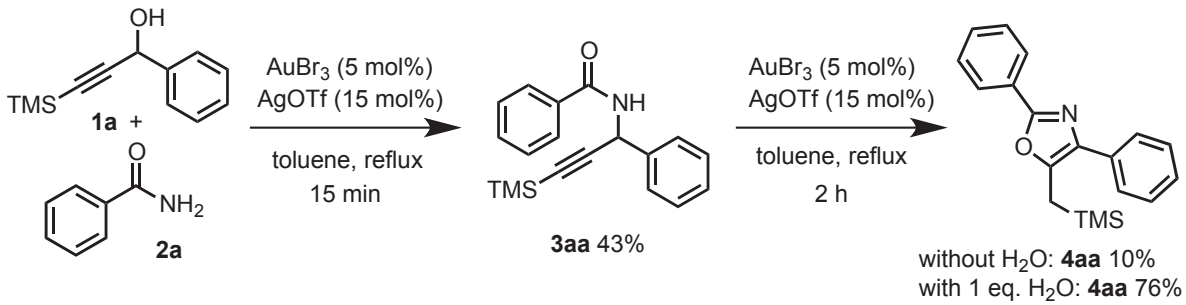
Scheme 4

We next tried the reaction of propargylic alcohol **1d** bearing a phenyl group at the alkynic terminus instead of the trimethylsilyl group of **1a,b** (Scheme 5). The reaction of **1d** with *p*-tolylamide (**2b**) gave the propargylic substitution product **3db** in a high yield without any formation of the corresponding oxazole **4db**, which shows that the trimethylsilyl group of **1a,b** is important for the cycloisomerization step.



Scheme 5

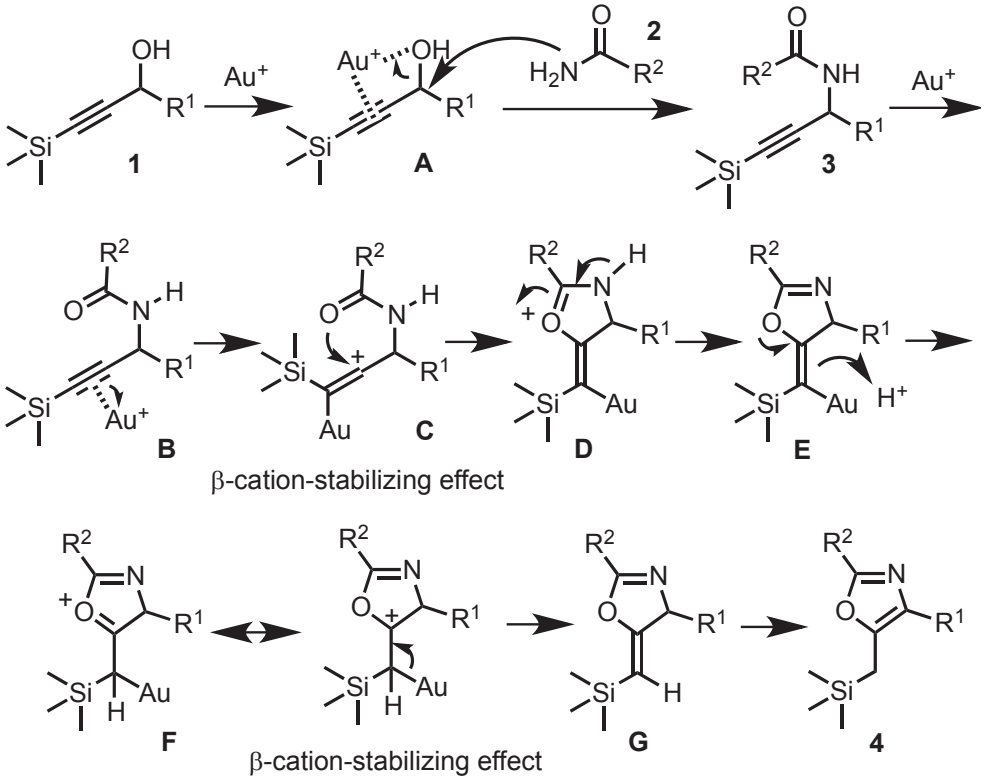
To confirm the reaction pathway, we examined the reaction of 3-trimethylsilylpropargylic alcohol **1a** and benzamide (**2a**) in the presence of 5 mol% of $AuBr_3$ and 15 mol% of AgOTf in toluene at reflux for 15 min, which afforded propargylic substitution product **3aa** in 43% yield (Scheme 6). Although the reaction of propargyl amide **3aa** with 5 mol% of $AuBr_3$ and 15 mol% of AgOTf in refluxing toluene without any additive afforded the oxazole **4aa** in low yield, the addition of 1 eq. H_2O to the reaction dramatically promoted the cycloisomerization to give oxazole **4aa** in good yield. These experiments clearly indicate that the reaction proceeds via propargylic substitution product **3aa** as an intermediate and that the trimethylsilyl group in **3aa** and H_2O molecule accelerate the cyclization step.



Scheme 6

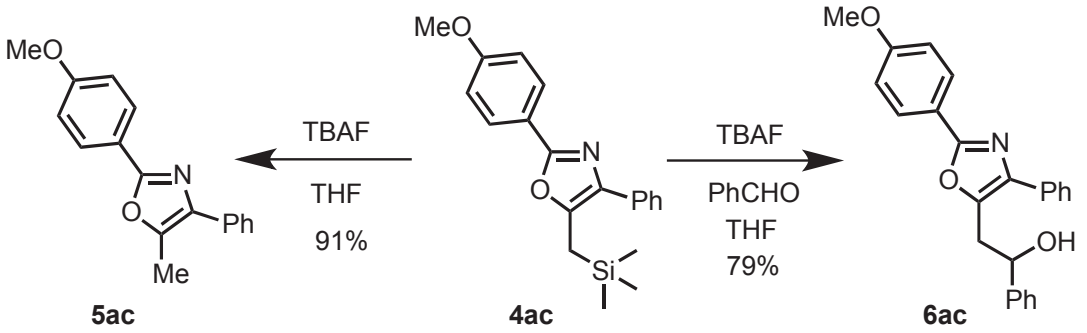
A plausible mechanism of the gold-catalyzed one-pot synthesis of substituted oxazoles **4** from propargylic alcohols **1** and amides **2** is shown in Scheme 7. Cationic gold species generated by gold catalyst and silver catalyst would coordinate to the triple bond and oxygen atom of the hydroxyl group of propargylic alcohol **1**[8-12] to promote propargylic substitution (**1**→**A**→**3**). The propargylic substitution

product **3** would be transformed into gold species **E** via cyclization involving the oxygen atom of the amide of **3** (**B→C→D→E**).[15] Notably, the β-cation-stabilizing effect of silicon[13] at the terminal position is important for the cyclization to **E**, since no oxazole was formed when 3-phenylpropargylic alcohol **1d** was used in place of 3-trimethylsilylpropargylic alcohol **1a,b** (Scheme 5). In addition, the β-cation-stabilizing effect of silicon[13] at the terminal position is important for the deauration step (**E→F→G**). Finally, intermediate **G** undergoes isomerization to give oxazoles **4**. Although the exact role of water molecule remains unclear, one possibility would be that the water molecule plays a role as the career of proton in the reaction.



Scheme 7

The trimethylsilylmethyl group in oxazoles **4** synthesized in this procedure is a very useful functionality for further elaboration (Scheme 8). For example, the treatment of oxazole **4ac** with TBAF in THF afforded oxazole **5ac** in 91% yield. Moreover, the reaction of oxazole **4ac** with TBAF[16] in the presence of benzaldehyde in THF furnished oxazole **6ac** in 79% yield. The hydroxyl group of **6ac** also affords a high degree of freedom for additional transformations if required.



Scheme 8

In summary, we present a gold-catalyzed synthesis of substituted oxazoles **4** from 3-trimethylsilylpropargylic alcohols **1** and amides **2** via propargylic substitution followed by cycloisomerization in one pot. The β-cation-stabilizing effect of the silicon atom of propargylic alcohol **1** is important for the cycloisomerization. Further synthetic use of TMS group in the products **4** and the role of water in the reaction will be reported elsewhere.

ACKNOWLEDGEMENTS

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14. Procedure for the synthesis of 2,4-diphenyl-5-[(trimethylsilyl)methyl]oxazole (**4aa**): $AuBr_3$ (5.4 mg, 0.012 mmol, 5 mol%) and AgOTf (9.4 mg, 0.037 mmol, 15 mol%) were added to a solution of 3-trimethylsilylpropargylic alcohols **1** (50 mg, 0.25 mmol) and benzamide (**2a**) (36 mg, 0.29 mmol) in toluene (3 mL) at room temperature and the mixture was heated at reflux. After complete consumption of propargylic substitution product **3aa** (the reaction was monitored by thin layer chromatography), the solvent was removed in vacuo and the crude product was subjected to column chromatography on silica gel (hexane:AcOEt = 30:1) to give 2,4-diphenyl-5-

[(trimethylsilyl)methyl]oxazole (**4aa**) (53 mg, 75%) as colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07-8.03 (2H, m), 7.75-7.72 (2H, m), 7.48-7.40 (5H, m), 7.33-7.26 (1H, m), 2.41 (2H, s), 0.14 (9H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.7, 147.2, 134.3, 132.9, 129.7, 128.7, 128.5, 127.8, 127.0, 126.7, 125.9, 16.5, -1.1.

15. In the cyclization step, an allene intermediate can also be considered. See, ref. 5.
16. The reaction was conducted with the TBAF dried by MS4A for a week.