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Metal-Free Azidation of α-Hydroxy Esters and α-Hydroxy Ketones Using Azidotrimethylsilane

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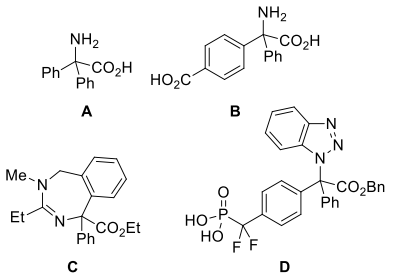
Abstract: We herein report a commercially available perchloric acid catalyst capable of catalyzing the azidation of α-hydroxy esters, α-hydroxy ketones and taddols using azidotrimethylsilane in dichloromethane at room temperature. Various substituted tertiary alcohols are well tolerated in this reaction. C^{α}-tetrasubstituted α-amino acid derivatives were prepared by one-pot sequential azidation and hydrogenation procedure. The advantage of this newly developed method includes operational simplicity, ready availability of catalyst, scale-up ability, and also good functional group compatibility.

Keywords: Azidation; α-Hydroxy esters; α-Hydroxy ketones; C^{α}-tetrasubstituted α-amino acids; S_N1 mechanism

Amino acids and their derivatives play an important role in the improvement of life due to their wide applications in medicine, pharmacology, nutrition and so on.[1] In this scenario, non-proteinogenic C^{α}-tetrasubstituted α-amino acids are in particular useful in biochemical researches.[2] Such C^{α}-tetrasubstituted α-amino acids represent a type of prominent structural scaffolds widely present in drugs, pharmaceutically and biochemically active compounds (Scheme 1). For example, 2,2-diphenylglycine **A**[3a] has antibacterial and antifungal properties, and its analogue **B**[3b] has antagonist activity at group I metabotropic glutamate receptors expressed in CHO cells. In addition, compounds fused with C^{α}-tetrasubstituted α-amino acid motifs also exhibit unique bioactivities and important applications. 4,5-Dihydro-1H-2,4-benzodiazepine **C**[3c] has antiarrhythmic activity and multi-functionalized compounds **D**[3d] could serve as effective PTP-1B inhibitors. Therefore, it is very much in demand to develop operationally simple and efficient protocols for the catalytic synthesis of C^{α}-tetrasubstituted α-amino acid derivatives.

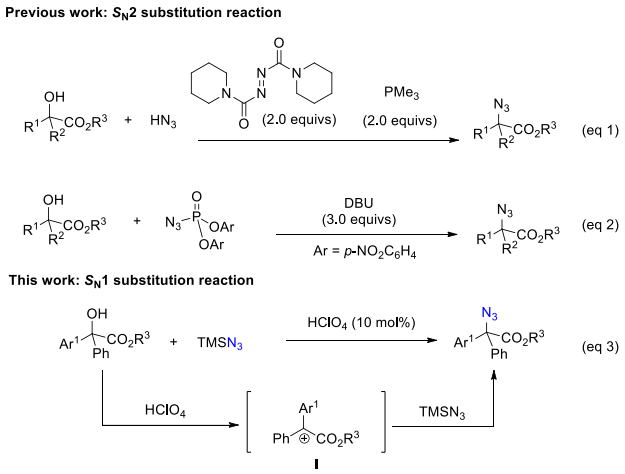
During the past decades, several elegant methods have been developed for the facile synthesis of C^{α}-tetrasubstituted α-amino acid derivatives,[4] including the Strecker reaction of ketimines,[5] the addition of nucleophiles to ketimines derived from α-ketoesters,[6] and electrophilic amination of active methines and their equivalents.[7] Despite ongoing progresses, it is still necessary and important to exploit new synthetic strategies.



Scheme 1. Representative bioactive compounds containing C^{α}-tetrasubstituted α-amino acid scaffold.

Very recently, catalytic functionalization of α-tertiary hydroxy esters emerges as a fruitful method for the diverse synthesis of carbonyl compounds with an α-fully substituted carbon.[8] The direct azidation of such α-hydroxy esters provided a facile access to α-tertiary azides featuring an ester group as precursors to C^{α}-tetrasubstituted α-amino acid derivatives,[9] but remained largely undeveloped.[10] In 2009, O'Donnell & McCarthy reported an elegant Mitsunobu reaction of α-tertiary hydroxy esters using HN_3 as the azide reagent (eq 1, Scheme 2).[11] However, it inevitably produced stoichiometric amount of waste hydrazine-1,2-dicarboxylates and tertiary phosphine oxides. Recently, Matsugi & Shioiri reported a S_N2 type azidation using bis(*p*-nitrophenyl)phosphorazidate (*p*-NO_2DPPA) as the azide agent, but this method required the use of three equivalents of DBU, leading to the formation of significant amount of waste (eq 2).[12] In addition, because these protocols involved a S_N2 displacement at the tetrasubstituted carbon, sterically congested α,α-diaryl α-tertiary hydroxy esters are often difficult substrates. On the other hand, the corresponding S_N1 azidation would be more sterically favourable, due to the formation of carbocation intermediates, however, it remains

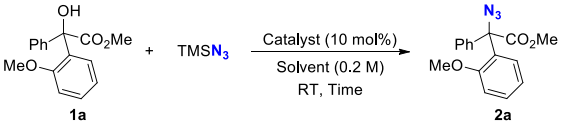
unexplored. This is possibly because the electron-withdrawing effect of the ester group makes it difficult to generate the carbocation intermediates. With our continuation in catalytic functionalization of tertiary alcohols bearing an α-electron-withdrawing group,[13] we have developed a Friedel-Crafts reaction of α-tertiary hydroxy esters with electron-rich arenes to furnish α-quaternary esters and ketones,[13a-c] along with several S_N1 type substitution reactions of 3-aryl-3-hydroxy oxindoles.[13d-f] On the basis of these work, we attempt to develop a catalytic azidation of α-tertiary hydroxy esters and $TMSN_3$. We speculate that this should be an attractive method for the synthesis of α,α-diaryl C^{α}-tetrasubstituted α-amino esters, as the two aryl substituents are helpful in stabilizing the carboncation intermediates. Such a S_N1 azidation is not only complementary to the S_N2 reaction, but has an obvious advantage of improved atom-economy, because of its much less waste generation. Herein, we wish to report that cheap and easily available $HClO_4$ (70%, aq) is identified as a powerful metal-free catalyst for the desired azidation reaction (eq 3).



Scheme 2. The azidation of α-hydroxy esters.

For initial investigation, we first conducted the reaction of model substrate **1a** with trimethylsilyl azide ($TMSN_3$) in dichloromethane by using various metal triflates as catalysts. Without the existence of catalyst, the reaction didn't proceed at all (Table 1, entry 1). Acid catalyst is essential for this reaction because it plays an important role to activate the tertiary alcohol substrate to produce the carbocation intermediate.[8a] We had previously found that $Ga(OTf)_3$ could efficiently catalyze the substitution reaction of 3-hydroxy oxindoles and $TMSN_3$,[13f] so we first tried it in the azidation of α-hydroxy ester **1a**. To our delight, the desired product **2a** was isolated in 77% yield (entry 2). Encouraged by this result, a series of metal triflates were then examined in order to achieve a higher catalytic ability. $Bi(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$ and AgOTf were found to be effective to yield the corresponding product in better yields (entries 3-6). However, no reaction took place when $Ba(OTf)_2$ and $Hg(OTf)_2$ were used as catalyst (see the Supporting Information, Table S1). Furthermore, Brønsted acids such as HOTf and $HClO_4$ (70%, aq) were viable catalysts for this reaction (entries 7-8). Remarkably, $HClO_4$ was an extremely reactive catalyst, as it mediated the reaction to finish within only 30 minutes to generate product **2a** in 96% yield (entry 8). This is a very exciting result, because the use of 70% aqueous solution of $HClO_4$ as the catalyst is safe and operationally very simple. Different solvents such as *n*-hexane, Et_2O, toluene were investigated, and CH_2Cl_2 was found to be the optimal solvent (entries 8-11). Reducing the amount of azide reagent $TMSN_3$ caused an obvious decrease in yield (entries 12-13). Comparable result was observed when the reaction concentration was increased (entry 14). Therefore, the optimized reaction conditions were determined to run the reaction at room temperature in CH_2Cl_2 with 3.0 equivs of $TMSN_3$, using10 mol% $HClO_4$ as catalyst.[14]

Table 1. Optimization of reaction conditions.[a]



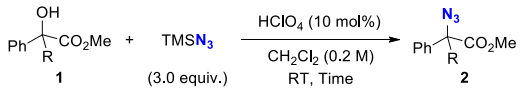
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	-	CH_2Cl_2	30	NR[c]
2	$Ga(OTf)_3$	CH_2Cl_2	30	77
3	$Bi(OTf)_3$	CH_2Cl_2	30	80
4	$Sn(OTf)_2$	CH_2Cl_2	30	86
5	$Cu(OTf)_2$	CH_2Cl_2	30	95
6	AgOTf	CH_2Cl_2	30	95
7	HOTf	CH_2Cl_2	30	93
8	**$HClO_4$**	**CH_2Cl_2**	**0.5**	**96**
9	$HClO_4$	*n*-Hexane	12	84
10	$HClO_4$	Et_2O	12	89
11	$HClO_4$	Toluene	12	92
12[d]	$HClO_4$	CH_2Cl_2	2	82
13[e]	$HClO_4$	CH_2Cl_2	2	68
14[f]	$HClO_4$	CH_2Cl_2	0.2	89

[a] Reaction were run with **1a** (0.2 mmol), $TMSN_3$ (3.0 equiv.), catalyst (10 mol%), solvent (1.0 mL), RT, stirred for a specified time.
[b] Isolated yield.
[c] No reaction.
[d] $TMSN_3$ (2.5 equiv.) was used.
[e] $TMSN_3$ (2.0 equiv.) was used.
[f] CH_2Cl_2 (0.5 mL) was used.

With the optimal reaction conditions in hand, we tested the substrate scope of α-hydroxy esters **1**. This reaction showed good functional group compatibility, as demonstrated in Table 2. Different substituents on the benzene ring such as methyl, methoxyl were well tolerated, affording the corrsponding products (**2a-2c**,

2e-**2g**) in moderate to good yields. Substrates bearing *ortho* or *para* substituent on the phenyl ring adjacent to the quaternary carbon were more reactive than the *meta* substituted one (entries 1 and 3 vs entry 2). Besides, the reaction of alcohol **1d** showed decreased reactivity (entry 4). Electron donating groups seem to be effective to enhance the reaction rate, probably due to their contribution for the stabilization of the posssible carbocation intermediates. As expected, alcohols **1h-j** with electron withdrawing groups on the phenyl ring showed lower activity, giving azidation products in moderate to excellent yield (entries 8-10). Almost no reaction occurred when trifluoromethyl substituted substrate **1k** was used (entry 11). These results indicate that an S_N1 reaction might take place in the presence of strong Brønsted acid. It's noteworthy that naphthyl and thiophenyl substituted α-hydroxy esters **1l-n** are also compatible substrates (entries 12-14). Attempts to use methyl substituted alcohol **1o** failed under the optimized reaction conditions (entry 15).

Table 2. Substrate scope of α-hydroxy esters.[a]

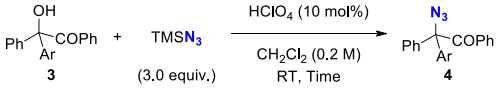


Entry	**1**: R	**2**	Time (h)	Yield (%)[b]
1	**1a**: 2-OMeC$_6$H$_4$	**2a**	0.5	83
2	**1b**: 3-OMeC$_6$H$_4$	**2b**	24	77
3	**1c**: 4-OMeC$_6$H$_4$	**2c**	0.5	89
4	**1d**: Ph	**2d**	10	76
5	**1e**: 2-MeC$_6$H$_4$	**2e**	0.5	84
6	**1f**: 3-MeC$_6$H$_4$	**2f**	11	79
7	**1g**: 4-MeC$_6$H$_4$	**2g**	5	75
8	**1h**: 4-FC$_6$H$_4$	**2h**	46	94
9	**1i**: 4-ClC$_6$H$_4$	**2i**	51	51
10	**1j**: 4-BrC$_6$H$_4$	**2j**	77	58
11	**1k**: 4-CF$_3$C$_6$H$_4$	**2k**	51	trace
12	**1l**: 1-Naphthyl	**2l**	18	81
13	**1m**: 2-Naphthyl	**2m**	24	70
14	**1n**: 2-Thiophenyl	**2n**	23	53
15	**1o**: Me	**2o**	24	mess

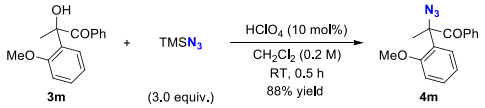
[a] Reaction conditions: α-hydroxy esters **1** (0.5 mmol), $TMSN_3$ (3.0 equiv.), $HClO_4$ (70%, aq, 10 mol%), CH_2Cl_2 (2.5 mL), RT, stirred for a specified time.
[b] Isolated yield.

We were delighted to find that this reaction is not only suitable for α-tertiary hydroxy esters, but also workable to α-tertiary hydroxy ketones **3** (Table 3). It shoud be noted that the azidation of α-tertiary hydroxy ketones were demonstrated as unsucessful example in Matsugi & Shioiri's report.[12] Previously, although Singh reported a $InBr_3$-catalyzed version of this reaction,[15] the development of a metal-free version was still necessary, considering the importance of the resulting α-azide ketones **4**.[16] The substrate scope is shown in Table 3. α-Tertiary hydroxy ketones **3a-c** and **3d-f**, with a methoxyl or a methyl substituent at *ortho*, *meta* or *para* position of the phenyl ring were all viable substrates, furnishing the desirsed adducts in good to high yield (entries 1-6). Those (**3g-i**) bearing an electron withdrawing group (F, Cl, Br) also worked well to give the desired products **4g-i** (entries 7-9). Diphenyl and naphthyl substituted tertiary alchols could be smoothly azidated to give the desired poducts **4j** and **4k** in 77% and 80% yield, respectively (entries 10-11). Tertiary alchol **3l** with a α-thiophenyl group worked inefficiently under our condition, giving the product **4l** in only 23% yield (entry 12). It's remarkable that various aromatic groups can be tolerated. Comparing with Singh's work,[15] our method could succesfully achieve the azidation of α-tertiary hydroxy ketones **3g-i** bearing an electron withdrawing group (F, Cl, Br) and tertiary alchol **3l** with a α-thiophenyl group rather than previous report. Besides, the $HClO_4$ (70%, aq) catalyst used in our method was much more available than $InBr_3$. It's worth to note that the substrate **3m** bearing a methyl group could also be workable to give the desired product **4m** in 88% yield.

Table 3. Substrate scope of α-hydroxy ketones.[a]



Entry	**3**: Ar	**4**	Time (h)	Yield (%)[b]
1	**3a**: 2-OMeC$_6$H$_4$	**4a**	42	87
2	**3b**: 3-OMeC$_6$H$_4$	**4b**	1	69
3	**3c**: 4-OMeC$_6$H$_4$	**4c**	1.5	64
4	**3d**: 2-MeC$_6$H$_4$	**4d**	18	76
5	**3e**: 3-MeC$_6$H$_4$	**4e**	5	65
6	**3f**: 4-MeC$_6$H$_4$	**4f**	5	75
7	**3g**: 4-FC$_6$H$_4$	**4g**	18	90
8	**3h**: 4-ClC$_6$H$_4$	**4h**	15	77
9	**3i**: 4-BrC$_6$H$_4$	**4i**	11	77
10	**3j**: 4-PhC$_6$H$_4$	**4j**	10	77
11	**3k**: 2-Naphthyl	**4k**	17	80
12	**3l**: 2-Thiophenyl	**4l**	1	23



[a] Reaction conditions: α-hydroxy ketones **3** (0.5 mmol), $TMSN_3$ (3.0 equiv.), $HClO_4$ (70%, aq, 10 mol%), CH_2Cl_2 (2.5 mL), RT, stirred for a specified time.
[b] Isolated yield.

Tertiary alcohols bearing other electron withdrawing groups, such as trifluoromethyl, difluoromethyl and acetyl group, were also viable substrates, if 100 mol% of $HClO_4$ was used as the

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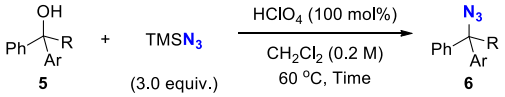
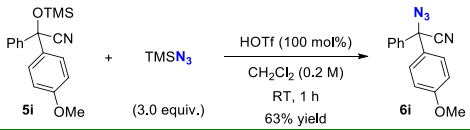
catalyst, as shown in Table 4. The trifluoromethyl substituted alcohols **5a-5c**, with a methoxyl substituent at *ortho*, *meta* or *para* position of the phenyl ring afforded the desired products **6a-6c** in 49-54% yields (entries 1-3). The alcohol **5d** bearing a chloro substituent on the phenyl ring showed lower activity, furnishing product **6d** in only 37% yield (entry 4). The tertiary alcohol **5e** with two methoxyl substituents on the *ortho* and *para* position of the phenyl ring showed higher activity, affording the corrsponding product **6e** in 50% yield (entry 5). The difluoromethyl substituted alcohols **5f** and **5g**, with a methoxyl substituent at *ortho* or *para* position of the phenyl ring also worked well to give the corresponding products **6f** and **6g** in 48% and 66% yield, respectively (entries 6-7). The tertiary alcohol **5h** bearing an acetyl group worked inefficiently under this condition, giving product **6h** in only 13% yield (entry 8). We also found that *O*-TMS cyanohydrin **5i** could also give the desired azide **6i** in 63% yield, if using 100 mol% of HOTf as the catalyst (we tried the removal of the TMS group of **5i** using TBAF, but only recovered the corresponding ketone).

Table 4. Substrate scope of other tertiary alcohols.[a]

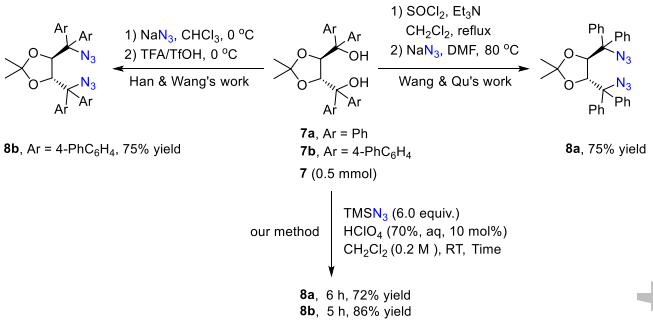


Entry	5	R	Ar	6	Time (h)	Yield (%)[b]
1	**5a**	CF_3	2-$OMeC_6H_4$	**6a**	72	49
2[c]	**5b**	CF_3	3-$OMeC_6H_4$	**6b**	72	49
3	**5c**	CF_3	4-$OMeC_6H_4$	**6c**	72	54
4[c]	**5d**	CF_3	4-ClC_6H_4	**6d**	72	37
5	**5e**	CF_3	2,4-$(OMe)_2C_6H_3$	**6e**	24	50
6	**5f**	CF_2H	2-$OMeC_6H_4$	**6f**	72	48
7	**5g**	CF_2H	4-$OMeC_6H_4$	**6g**	36	66
8	**5h**	Ac	2-$OMeC_6H_4$	**6h**	0.5	13



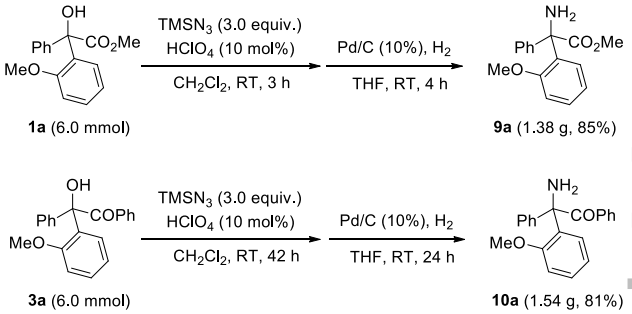
[a] Reaction conditions: tertiary alcohols **5** (0.5 mmol), $TMSN_3$ (3.0 equiv.), $HClO_4$ (70%, aq, 100 mol%), CH_2Cl_2 (2.5 mL), 60 °C, stirred for a specified time.
[b] Isolated yield.
[c] $TMSN_3$ (5.0 equiv.) was used.

Our method is also workable for the azidation of tertiaryl alcohols without an α-electron-withdrawing group, as shown by the facile synthesis of taddol derived diazides **8**. As shown in Scheme 3, under our condition, taddols **7a** and **7b** readily provided the desired diazides **8a** and **8b** in 72% and 86% yield, respectively. Diazides **8** have wide applications in asymmetric synthesis as chiral reagents or for the design of new ligands and organocatalysts.[17] Comparing with Wang & Qu's work [18a] as well as Han & Wang's work,[18b] hydrazoic acid and sodium azide were used, so the reaction must be conducted very carefully with strict protection. In contrast, only simple operation was adopted in our newly developed method (Scheme 3).



Scheme 3. Modification of taddol derivatives.

This azidation method could be readily scaled up, as evidenced by the gram scale synthesis of C^{α}-tetrasubstituted α-amino acid derivatives **9a** and **10a** in a one-pot manipulation. The azidation of **1a** or **3a** were performed on a 6.0 mmol scale, followed by the Pd-catalyzed hydrogenation of the crude mixtures to give α-amino ester or ketone **9a** and **10a** in 85% and 81% isolated yield, respectively (Scheme 4).



Scheme 4. Gram scale synthesis of amino acid derivatives.

In conclusion, we have developed a highly efficient $HClO_4$ catalyzed azidation reaction of α-tertiary hydroxy esters and α-tertiary hydroxy ketones using $TMSN_3$ for the synthesis of C^{α}-tetrasubstituted α-amino acid derivatives. Various substituted starting materials could be applied under the optimized conditions. Notably, the use of 70% aqueous solution of $HClO_4$ as the catalyst is safe and operationally very simple, and importantly, free of the contamination of transition metals with the final adducts that are valuable targets in medicinal researches.

Experimental Section

To a solution of α-hydroxy esters **1** or α-hydroxy ketones **3** (0.5 mmol) in dry CH_2Cl_2 (2.5 mL) was added $HClO_4$ (70%, aq, 0.05 mmol) and $TMSN_3$ (1.5 mmol) into 5.0 mL vial under air, and the reaction mixture was stirred at room temperature until complete consumption as monitored by TLC analysis. The solvents were removed under reduced pressure,

and column chromatography was used to give the desired product α-azide esters **2** or α-azide ketones **4**.

Acknowledgements

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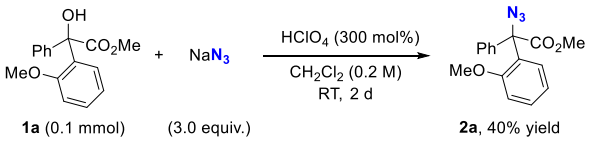
[14] As kindly suggested by one of the reviewers, we also tried using the much cheaper NaN_3 rather than $TMSN_3$ as the azide reagent, but no reaction occurred in the presence of 10 mol% $HClO_4$. By increasing the amount of $HClO_4$ to 300 mol%, the desired product **2a** could be obtained in 40% yield.



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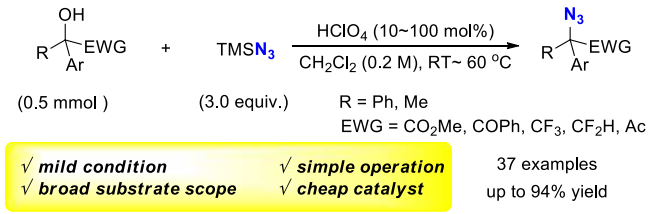
Metal-Free Azidation of α-Hydroxy Esters and α-Hydroxy Ketones Using Azidotrimethylsilane



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