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Copper Triflate Catalyzed Oxidative α-Allylation of Glycine Derivatives

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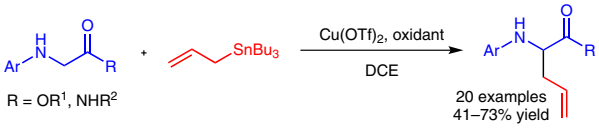

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Abstract Copper triflate catalyzed oxidative C–H functionalization of glycine derivatives with allyltributyltin has been established using oxygen or *tert*-butyl hydroperoxide as oxidant. Various glycine esters and glycine amides were suitable substrates for this oxidative allylation reaction and afforded the desired homoallylic amines in moderate to good yields.

Key words copper triflate, glycine derivatives, allylation, homoallylic amines, oxygen, TBHP

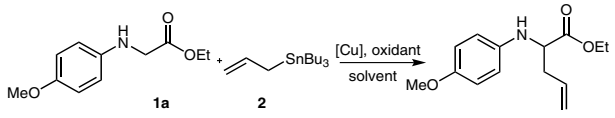
The oxidative coupling-cross of C–H bonds has emerged as an effective and straightforward protocol to construct new C–C bonds as it avoids prefunctionalization of substrates and is more atom economic and environmentally friendly.[1] In particular, the oxidative C–H functionalization of glycine derivatives with various nucleophiles has proved to be a convenient way to synthesize diverse α-substituted α-amino derivatives, which are of great importance and have applications in the synthesis of biologically active drugs and natural products.[2] The prominent route appears to be the selective oxidation of C–H bond adjacent to the nitrogen atom to generate a reactive iminium ion, which upon deprotonation gives the imine intermediate and then reacts with a nucleophile to form a new C–C bond. In 2008, Li et al.[2a] reported the pioneering work on the copper-complex-catalyzed α-alkylation of glycine derivatives with malonates. Then structurally diverse nucleophiles, such as ketones,[3] ethers,[4] indoles,[5] phenols,[6] alkynes,[7] and methylquinolines[8] have also been successfully explored for this transformation in suitable catalytic systems.

Homoallylic amines are useful building blocks for many biologically active compounds and nitrogen-containing natural products, because their double bond of allylic group can be furtherly modified into various functional groups.[9] The most commonly used pathway for the synthesis of homoallylic amines is the addition of allyl metal reagents to imine substrates.[10] However, since some imine substrates are difficult to prepare or unstable, this method still suffered from some shortages. Due to the importance of these structural motifs, there is a continuing demand for the development of new and convenient pathways for the synthesis of homoallylic amine compounds, such as the oxidative cross-coupling between C–H bonds. In 2010, Kumaraswamy et al.[11] firstly reported the oxidative α-allylation of *N*-aryl tetrahydroisoquinoline with allyltributyltin catalyzed by $FeCl_3·6H_2O$ in the presence of TBHP. Inspired by this work, in 2016, Wang et al.[12] disclosed a silver triflate catalyzed cascade of in situ oxidation and allylation of arylbenzylamines employing 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate as oxidant. However, reports about the oxidative allylation of glycine derivatives are still rare.[13] Owing to the biological importance of homoallylic amines and α-amino acid derivatives, we carried out the investigation on oxidative C–H functionalization reaction of glycine derivatives with allyltributyltin catalyzed by a copper salt to produce α-allyl glycine derivatives.

Initially, *N*-PMP (*p*-methoxyphenyl) glycine ester (**1a**) and allyltributyltin (**2**) were chosen as model substrates to explore and optimize the experimental conditions. When the reaction was performed in the presence of 10 mol% $CuCl_2$ under an oxygen atmosphere at 40 °C, the desired α-allyl glycine ester **3a** was isolated in 36% yield (Table 1, entry 1). Then, several other copper salts were investigated to improve the reaction yields and $Cu(OTf)_2$ proved to be best with 73% yield (Table 1, entries 2–4). Notably, replacing molecular oxygen with air gave an inferior result (Table 1, entry 5). A number of other oxidants were subsequently screened (Table1, entries 6–8) and a stoichiometric amount of TBHP exhibited superior yields than O_2 (75% vs. 73%).

However, given the economic and environmental factors, molecular oxygen was chosen as the terminal oxidant for the oxidative C–H functionalization of glycine derivatives with allyltributyltin. Lowering the temperature to 25 °C or raising the temperature to 60 °C was not beneficial to the oxidative reaction (Table 1, entries 9 and 10). Examination of solvent effects showed that DCE was the best solvent and gave 73% yield of the corresponding product. Based on above results, the optimized reaction should be performed with 10 mol% of $Cu(OTf)_2$ in DCE at 40 °C using molecular oxygen (1.0 atm) as terminal oxidant.

Table 1 Optimization of Conditions[a]



Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	$CuCl_2$	O_2	DCE	36
2	$CuBr_2$	O_2	DCE	41
3	$Cu(OAc)_2$	O_2	DCE	47
4	$Cu(OTf)_2$	O_2	DCE	73
5	$Cu(OTf)_2$	air	DCE	17
6	$Cu(OTf)_2$	TBHP	DCE	75
7	$Cu(OTf)_2$	DTBP	DCE	44
8	$Cu(OTf)_2$	DDQ	DCE	63
9[c]	$Cu(OTf)_2$	O_2	DCE	25
10[d]	$Cu(OTf)_2$	O_2	DCE	64
11	$Cu(OTf)_2$	O_2	CH_2Cl_2	67
12	$Cu(OTf)_2$	O_2	PhMe	58
13	$Cu(OTf)_2$	O_2	THF	51
14	$Cu(OTf)_2$	O_2	MeCN	46

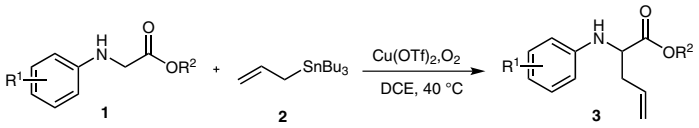
[a] Reaction conditions: **1a** (0.2 mmol) and catalyst (10 mol%) in solvent (1.0 mL) at 40 °C for 4 h, under O_2 (1 atm) or using oxidant (1.0 equiv); followed by the addition of **2** (0.24 mmol) for another 6 h.
[b] Isolated yield.
[c] At 25 °C.
[d] At 60 °C.

With the optimal conditions in hand, the scope of *N*-aryl glycine esters for the $Cu(OTf)_2$-catalyzed aerobic α-allylation was explored (Table 2).[14] The electronic effect of substituents on the *N*-aryl moiety of glycine esters was initially studied. A range of *N*-aryl glycine esters **1a–1b** bearing electron-donating groups and those bearing electron-withdrawing groups on the *N*-aryl ring (**1d–f**) were all tolerated and afforded the desired coupling products **3a–f** in satisfactory yields (Table 2, entries 1–6). Gratifyingly, halogen atoms (F, Cl, and Br) could be tolerated well, thereby making this methodology more useful for further transformations at the halogenated position (Table 2, entries 4–6). The methyl group on the *ortho* position resulted in lower yield than that on the *para* and *meta* position, indicating that steric effects had an obvious effect on the yields of the allylation reaction (Table 2, entries 2 vs. 7 vs. 8). The steric substituent effects of the ester moiety were then investigated. When the corresponding methyl ester **1i** was employed instead of ethyl ester **1a**, coupling products **3i** were also isolated in 72% yield (Table 2, entry 9). However, when a *tert*-butyl ester **1j** was utilized, the reaction did not proceed at all under the optimal conditions, which could be attributed to the steric hindrance of *tert*-butyl group (Table 2, entry 10).

After the scope of *N*-aryl glycine esters was examined, a series of *N*-aryl glycine amides were investigated. Unfortunately, only 14% yield of the desired product **3k** was observed when *N*-PMP glycine amide **1k** was applied under the optimized conditions. Replacing molecular oxygen with TBHP led to a significant improvement on the yield when lowering the reaction temperature to 25 °C (Table 3, entry 1). Thus the oxidative allylation of *N*-glycine amides was conducted in the presence of $Cu(OTf)_2$ and TBHP.[15] The electronic and steric variations in the *N*-aryl moiety of glycine amides were also tested. Similarly to glycine esters, both electron-rich and electron-deficient glycine amides reacted well and afforded the corresponding products in 63–75% yields (Table 3, entries 1–5). Gratifyingly, the presence of a methyl group at the *para*, *meta*, or *ortho* position was tolerated and afforded the desired α-allyl glycine amides in satisfactory yields (Table 3, entries 6 and 7). To establish the scope of this transformation further, various secondary amides were next investigated. The oxidative cross-coupling reaction of allyltributyltin with secondary amides, except the corresponding *tert*-butyl derivative, resulted in the desired *N*-aryl glycine amides in moderate yields (Table 3, entries 8–12).

Some control experiments were carried out in order to reveal the mechanism of this transformation (Table 4). When 2,6-di-*tert*-butyl-4-methylphenol (BHT), a radical scavenger, was added into the reaction system of *N*-PMP glycine derivatives **1a** and **1k** (Table 4, entries 1 and 4), the yields of coupling products **3a** and **3k** both dramatically decreased. This result suggests that reactions may undergo a radical mechanism. *N*-PMP glycine derivatives **1a** and **1k** could converted into the imine intermediates **4a** and **4k** in the presence of $Cu(OTf)_2$ and oxidant, respectively (Table 4, entries 2 and 5). The result in Table 4 (entry 3) indicated that $Cu(OTf)_2$ is involved in the oxidation process and the only role of oxygen is to reoxidative the reduced copper.[16] However, the result in Table 4 (entry 6) indicated that the terminal oxidant THBP not only involved in the reoxidation of copper but also in the oxidative process. With respect to the reaction with imine **4**, a diminished yield was observed in the absence of $Cu(OTf)_2$, implying that $Cu(OTf)_2$ should activate **4** for the nucleophilic attack (Table 4, entries 7 and 8).

Table 2 Scope of *N*-Aryl-Glycine Esters[a]

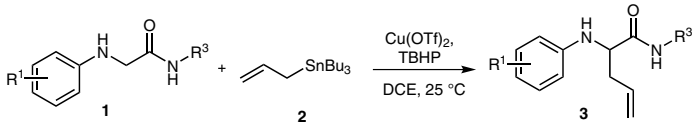


Entry	R^1	R^2	Product	Yield (%)[b]
1	4-MeO	Et	**3a**	73
2	4-Me	Et	**3b**	70
3	H	Et	**3c**	59
4	4-F	Et	**3d**	68
5	4-Cl	Et	**3e**	67
6	4-Br	Et	**3f**	62
7	3-Me	Et	**3g**	66
8	2-Me	Et	**3h**	43
9	4-MeO	Me	**3i**	72
10	4-MeO	*t*-Bu	**3j**	0

[a] Reaction conditions: glycine ester (0.2 mmol) and $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at 40 °C under O_2 (1.0 atm) for 4 h, followed by the addition of **2** (1.2 equiv) for another 6 h.
[b] Isolated yield.

Consequently, based on experimental observations and the literatures,[16] the plausible mechanism for this copper triflate catalyzed oxidative allylation of glycine derivatives in the presence of oxidant is illustrated (Scheme 1). In the catalytic system of $Cu(OTf)_2$ and molecular oxygen, initial oxidation of **1** by Cu(II) via single-electron transfer (SET)

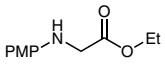
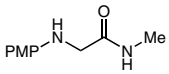
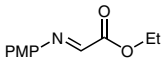
Table 3 Scope of *N*-Aryl Glycine Amides[a]



Entry	R^1	R^3	Product	Yield (%)[b]
1	4-MeO	Me	**3k**	73(14[c])
2	4-Me	Me	**3l**	68
3	H	Me	**3m**	63
4	4-F	Me	**3n**	71
5	4-Cl	Me	**3o**	75
6	3-Me	Me	**3p**	67
7	2-Me	Me	**3q**	65
8	4-MeO	Et	**3r**	57
9	4-MeO	*n*-Bu	**3s**	63
10	4-MeO	$C_{12}H_{25}$	**3t**	70
11	4-MeO	C_6H_{11}	**3u**	41
12	4-MeO	*t*-Bu	**3v**	trace[d]

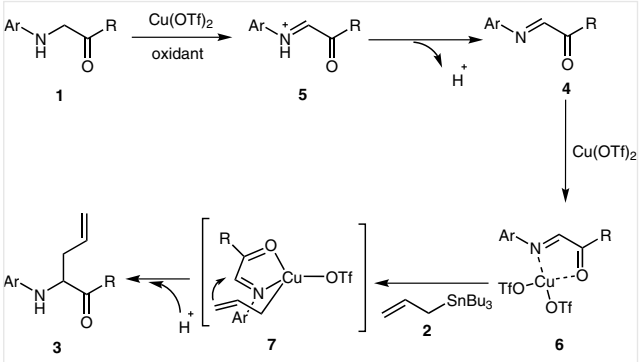
[a] Reaction conditions: glycine amides (0.2 mmol), TBHP (1.0 equiv 5.5 M in decane), and $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at r.t for 4 h, followed by the addition of **2** (1.2 equiv) for another 6 h.
[b] Isolated yield.
[c] The reaction was conducted under O_2 (1.0 atm) at 40 °C.
[d] Detected by GC–MS.

Table 4 Control Experiments

Entry	Substrate	Conditions[a]	Yield (%)[b]
1		A	trace
2		B	74[c]
3		C	0
4		D	trace
5		E	74[c]
6		F	43
7		G	11
8		H	84

[a] Conditions A: **1a** (0.2 mmol), BHT (2.0 equiv), $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at 40 °C under O_2 (1.0 atm) for 4 h, followed by the addition of **2** (1.2 equiv) for another 6 h; conditions B: **1a** (0.2 mmol), $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at 40 °C under O_2 (1.0 atm) for 4 h; conditions C: **1a** (0.2 mmol) in DCE (1.0 mL) at 40 °C under O_2 (1.0 atm) for 4 h; conditions D: **1k** (0.2 mmol), TBHP (1.0 equiv), BHT (2.0 equiv), $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at r.t. for 4 h, followed by the addition of **2** (1.2 equiv) for another 6 h; conditions E: **1k** (0.2 mmol), TBHP (1.0 equiv), $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at r.t. for 4 h; conditions F: **1k** (0.2 mmol), TBHP (1.0 equiv) in DCE (1.0 mL) at r.t. for 4 h; conditions G: **4a** (0.2 mmol), **2** (1.2 equiv) in DCE (1.0 mL) at r.t. for 6 h; conditions H: **4a** (0.2 mmol), **2** (1.2 equiv), $Cu(OTf)_2$ (10 mol%) in DCE (1.0 mL) at r.t. for 6 h.
[b] Isolated yield.
[c] Isolated yields of intermediate imines.

followed by a sequential proton and electron transfer leads to an iminium ion **5**.[17] On the other hand, when TBHP was utilized as the terminal oxidant, a *tert*-butoxyl radical generated by the copper-catalyzed decomposition of TBHP and then abstracted a hydrogen atom from **1** to form intermediate radical, which also converted into iminium ion **5** via single-electron transfer (SET).[3,18] Then iminium ion **5** furnish to imine **4** by deprotonation. A bidentate intermediate **6** was formed by the coordination of copper triflate to the imine intermediate **4**.[7b] Further, a *trans*-metalation takes place between the allyl-Sn reagent **2** and the intermediate **6** giving allylic copper complex **7**, followed by nucleophilic attack of allyl to imine generates the homoallylic amine **3**.



Scheme 1 Plausible mechanism for the oxidative allylation of glycine derivatives

In summary, a facile approach for copper triflate catalyzed oxidative C–H functionalization of glycine derivatives with allyltributyltin has been established using molecular oxygen or TBHP as oxidant catalyzed by a simple copper salt. Various glycine derivatives bearing electron-donating groups as well as electron-withdrawing groups underwent the oxidative allylation reaction smoothly and afforded the desired homoallylic amines in moderate to good yields.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588158.

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(14) **General Procedure for the Allylation of *N*-Aryl Glycine Esters 3a**
N-PMP glycine ester **1a** (0.2 mmol) and $Cu(OTf)_2$ (10 mol%) were reacted under oxygen atmosphere (1.0 atm) in DCE (1.0 mL) at 40 °C. After the glycine ester disappeared (by TLC), allyl-

tributyltin (**2**, 0.24 mmol) was added, and the mixture was stirred for another 6 h. After the reaction finished, the mixture was directly purified by flash chromatography to afford the desired product **3a**; 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 8.5 Hz, 2 H), 6.60 (d, *J* = 8.5 Hz, 2 H), 5.80 (td, *J* = 17.1, 7.2 Hz, 1 H), 5.25–5.11 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 4.05 (q, *J* = 6.3 Hz, 1 H), 3.91 (s, 1 H), 3.74 (s, 3 H), 2.58 (dq, *J* = 14.0, 6.9 Hz, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.64, 151.81, 139.75, 131.97, 117.83, 114.23, 113.90, 60.08, 56.27, 54.75, 36.23, 13.33. MS (EI): *m/z* =249 [M$^+$].

(15) **General Procedure for the Allylation of *N*-Aryl Glycine Amide 3k**

N-PMP glycine amide **1k** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), and TBHP (1.0 equiv, 5.5 M in decane) were reacted in DCE (1.0 mL) at r.t. After the glycine amide disappeared (by TLC), allytributyltin (**2**, 0.24 mmol) was added, and the mixture was stirred for another 6 h. After the reaction finished, the mixture was directly purified by flash chromatography to afford desired product **3k**; 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.89 (s, 1 H), 6.72 (d, *J* = 8.8 Hz, 2 H), 6.48 (d, *J* = 8.8 Hz, 2 H), 5.69 (td, *J* = 17.2, 7.2 Hz, 1 H), 5.21–5.05 (m, 2 H), 3.68 (s, 3 H), 3.66 (s, 1 H), 3.57 (d, *J* = 8.6 Hz, 1 H), 2.74 (d, *J* = 5.0 Hz, 3 H), 2.70 (dd, *J* = 10.0, 4.4 Hz, 1 H), 2.46–2.30 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 172.72, 152.31, 139.84, 133.03, 118.21, 114.03, 113.96, 58.15, 54.78, 36.91, 25.05. MS (EI): *m/z* = 234 [M$^+$].

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