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A silver triflate-catalyzed cascade of in situ-oxidation and allylation of arylbenzylamines

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ABSTRACT

A silver-triflate catalyzed cascade of in situ-oxidation and allylation of arylbenzylamines is reported. The 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate is employed as a mild oxidant which is compatible with both catalyst and ligand. Racemic BINAP is also utilized to assist with the catalyst in regulating the yields of products. Various homoallylic amines are obtained in 39–99% yields.

Introduction

Homoallylic amines are useful synthetic modules[1] since the double bond of the allylic group can be modified into various functional groups in further manipulations[2] toward synthesis of many useful amines. Owing to the advantage of homoallylic amines, chemists devoted their efforts to the synthetic research on this kind of compounds and have achieved fruitful results. So far as we know, there are three pathways popular (as shown in Scheme 1) to synthesize homoallylic amines: (1) Direct nucleophilic addition to imines using allylic metal reagents. This kind of reaction is the most commonly used pathway, which was studied thoroughly and widely. It has been well developed no matter in the choice of allylation reagents and catalytic systems,[4e] or the application in synthesis of natural products.[3] Moreover, considerable progress has been achieved in substrate scope, reaction activity, and stereo control.[4] On the other side, there are a few shortages: some imine substrates are unstable, which need to be prepared in situ; and a few imine substrates are difficult to prepare or hard to purify. (2) Using multicomponent reaction to make an aldehyde and an amine condense into an imine in situ, which is then subjected to the attack of allylation reagents. In this way, homoallylic amines can also be obtained,[5] and there are also numbers of reports and studies about this method. (3) Recently, using C–H bond oxidation[6] of α-position of the amino group to generate iminium cation in situ, which is available to accept the nucleophilic attack,[7] offers a brand new and convenient pathway for the synthesis of homoallylic amines. The nodus of this method is to solve the compatibility between oxidant, metallic catalyst, and ligand. By now, there is only one case using this method for the synthesis of homoallylic amine, it was reported by Pitchaiah's group in 2010 that $FeCl_3{\cdot}6H_2O$ catalyzed C1-achiral oxidative addition to N-aryl tetrahydroisoquinoline by allyl-tin reagent can work in the presence of T-HYDRO as oxidant.[8] In this reaction, an iminium cation intermediate was involved and the double bond of imine was activated to accept the attack of allyl-tin reagent. Consequently, homoallylic amine was obtained as a product. Inspired by this work on C–H oxidation, a silver triflate-catalyzed cascade of in situ-oxidation and allylation of arylbenzylamines using allyl-Si reagent is reported by our group.

Considered that allyl-Si reagents are less toxic and low priced, we chose allyl trimethoxylsilane as allylation reagent at first to carry out the study. Since we proposed to make the oxidation of amine and allylation of the α-position of amino group in one-pot reaction, the key problem is to find an oxidant that can be compatible with the catalytic system. Fortunately we find hydrogen accepting oxidant of T^+Y^- (TEMPO salts) type an ideal choice for us.[9] Employing *N*-phenylbenzylamine **2a** as substrate, we first tried some regular catalytic systems[10] (Table 1, entries 1–3), but no desired product was discovered. To simplify the reaction condition, we excluded ligand and additive from the reaction system and screened Lewis acids directly. Results show that CuOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, AgOTf, and AgF can all catalyze our reaction and give the corresponding allylation product **3a** (Table 1, entries 4–8).

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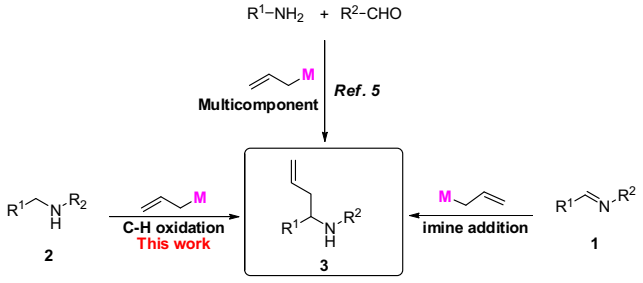
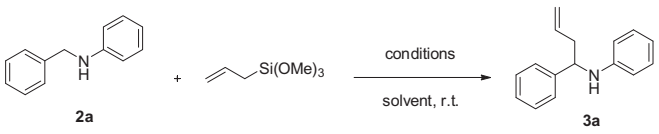


Scheme 1. Different strategies for the synthesis of homoallylamines.

Given that AgOTf is better than other Lewis acids, we further investigated some other silver salts (some selected cases are shown in Table 1, entries 8–11), but AgOTf still gives better behavior. Suppose that anion effect of OTf^- might be the key factor during the reaction course, we took three acidic additives (HOTf, Tf_2O, and TsOH) into investigation (see Table 1, entries 12–14). As expected, the yields of reactions have been improved further. Since H^+ might give assistance to the releasing of product, moreover, HOTf doesn't introduce any other anions into the reaction system compared to TsOH, we thus chose HOTf as the right additive for this reaction. To nail down the necessary factor of the reaction, we carried out control experiments[11] based on the existing conditions before further optimization. Results indicated that oxidant and AgOTf are necessary for our reaction. Next, we investigated the loading of AgOTf as well as reaction temperature. Observation showed that room temperature and 40 mol % of HOTf is the better choice (Table 1, entries 15 and 20). Additionally, prolonged reaction times brought about a decline of yield (Table 1, entry 21). Screening of solvents indicated that THF behaved better (Table 1, entries 11–19). At last, we tried to add some ligands into the reaction system (see SI for details), although any of these ligands gave chiral product, we pleasantly found that (*S*)-BINAP could improve the yield to 99% and shorten the reaction time to 15 h. Given that, we replaced (*S*)-BINAP with racemic BINAP and the yield remained 99%. In summary, we determined the optimal reaction conditions as follows: 10 mol % of AgOTf, 12 mol % of BINAP, 40 mol % of HOTf, 1.1 equiv of $T^+BF_4^-$, 2.0 equiv of allyltrimethoxysilane, keeping stirring for 15 h in THF at room temperature.

Table 1
Screening of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Additive	Ligand[b]	Yield[c]
1	CuCl	$T^+BF_4^-$	THF	TBAT	2,2′-bipy	N.D.
2	CuF_2	$T^+BF_4^-$	THF		2,2′-bipy	N.D.
3	AgF	$T^+BF_4^-$	THF		PPh_3	N.D.
4	$Cu(OTf)_2$[d]	$T^+BF_4^-$	THF			40%
5	CuOTf[d]	$T^+BF_4^-$	THF			47%
6	$Zn(OTf)_2$[d]	$T^+BF_4^-$	THF			44%
7	AgF[d]	$T^+BF_4^-$	THF			25%
8	AgOTf[d]	$T^+BF_4^-$	THF			57%
9	AgOTf[d]	$K_2S_2O_8$	THF			N.D.
10	AgOTf[d]	Oxone	THF			N.D.
11	AgOTf[d]	O_2	THF			N.D.
12	AgOTf[d]	DDQ	THF			Trace
13	AgOTf[d]	TBHP	THF			N.D.
14	AgOTf[d]	$PhI(OAc)_2$	THF			N.D.
15	$AgSbF_6$[d]	$T^+BF_4^-$	THF			N.D.
16	$AgNO_3$[d]	$T^+BF_4^-$	THF			21%
17	$AgBF_4$[d]	$T^+BF_4^-$	THF			14%
18	AgOTf	$T^+BF_4^-$	THF	HOTf		54%
19	AgOTf	$T^+BF_4^-$	THF	Tf_2O		22%
20	AgOTf	$T^+BF_4^-$	THF	TosOH		27%
21	AgOTf	$T^+BF_4^-$	THF	HOTf[e]		64%
22	AgOTf	$T^+BF_4^-$	CH_2Cl_2	HOTf[e]		30%
23	AgOTf	$T^+BF_4^-$	Toluene	HOTf[e]		12%
24	AgOTf	$T^+BF_4^-$	PhCl	HOTf[e]		39%
25	AgOTf	$T^+BF_4^-$	1,4-Dioxane	HOTf[e]		19%
26	AgOTf	$T^+BF_4^-$	THF	HOTf[e]		27%[f]
27	AgOTf	$T^+BF_4^-$	THF	HOTf[e]		59%[g]
28	AgOTf	$T^+BF_4^-$	THF	HOTf[e]	BINAP	99%[h]

[a] All the reactions were carried out using 0.2 mmol of **2a**, 0.22 mmol of $T^+BF_4^-$, 2 equiv of allylation reagent, 10 mol % of catalyst and 20 mol % of additives in 2 mL solvent at rt.
[b] The amount of ligand is 0.024 mmol.
[c] Isolated yield.
[d] 20 mol % of catalyst was added.
[e] 40 mol % HOTf was added.
[f] This reaction was carried out at 0 °C.
[g] Reaction time was 24 h.
[h] Reaction time was 15 h.

We firstly introduced some substitutions on the phenyl group. When the 4-position of the benzene ring was substituted, the reaction performed good (Table 2, entries 2–5); besides, when the 3-position or both the 3 and 4-position were substituted, the yield was still good (Table 2, entries 6–7). Next, we introduced different substitutions on the benzyl group and found that when the *para*-position of amino was substituted by methyl, halogens, or cyano groups, the reaction showed good to excellent yields (Table 2, entries 8–11 and 13); however, when the *para*-position was substituted by methoxyl or trifluoromethyl, the yields turned poor (Table 2, entries 12 and 14). In order to further expand the substrate scope, we also prepared a few substrates containing substituents on other positions of the benzyl group from available starting materials in our laboratory and obtained **3o**, **3p,** and **3q** as corresponding products with moderate to good yields (Table 2, entries 15–17). Generally, this reaction has good functional group tolerance, for instance, the acid-sensitive cyano group and unprotected phenolic hydroxyl group, they were not affected in any way during the reaction (Table 2, entries 13 and 15). We also tried to use 2-pyridinecarboxaldehyde, furfural, and 2-thenaldehyde as starting materials and synthesized the aromatic heterocyclic substrates **2r**, **2s,** and **2t**. Fortunately these substrates were all able to complete the reaction under standard condition and obtain the corresponding products **3r**, **3s,** and **3t** in moderate yields (Table 2, entries 18–20).

Furthermore, we found this reaction is also suitable for some amino acid and peptides [Scheme 2(a) and (b)] and achieved corresponding allylation products in moderate to good yields. For phosphoramide **2x**, a trace of allylated product was also observed [Scheme 2(c)].

With these conclusions in hand, we speculated a possible mechanism for the reaction (Fig. 1): initially, catalyst AgOTf coordinates with the ligand, then the allyl-Si reagent B is activated by OTf^- anion and a molecule of $(MeO)_3Si^+OTf^-$[12] is released. Simultaneously, a transmetallation takes place between the allyl-Si reagent and the Ag-ligand complex, giving allylic-silver complex **C**[13] as an active species. Next, **C** implements a nucleophilic addition to imine **A**, which is oxidized from **2a** in situ, and amino silver **D** is formed as an intermediate. Finally, under the action of H^+ provided by HOTf, a protonation occurs to intermediate **D** and gives **3a** as the target product.

Conclusion

Our group have established a one-pot reaction system for in situ-oxidation and allylation of arylbenzylamines. In this