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Direct amination of 2-(1-tosylalkyl)phenols with aqueous ammonia: a metal-free synthesis of primary amines

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ABSTRACT

A metal-free and concise method for the selective synthesis of primary amines directly from 2-(1-tosylalkyl)phenols with aqueous ammonia under mild conditions has been developed. In addition, primary amine could be conveniently converted to benzoxazinone in good yield.

Amines are a prominent class of organic compounds attributing to their remarkable significance in various biological active molecules, natural products, and industrial processes (agrochemicals, polymers, dyestuffs, pigments, emulsifiers, and plasticizing agents).[1] Among the different types of amines, primary amines are valuable synthetic intermediates for the further derivatization.[2] Since ammonia is one of the most intriguing amine sources from the cost and atom-economy point of view, the direct construction of primary amines from ammonia has attracted extensive attention in the past decades.[3] The most common routes for the preparation of primary amines from ammonia involve reductive amination of carbonyl compounds,[4] hydroamination of olefins,[5] hydroaminomethylation of alkenes,[6] and telomerization of dienes.[7] In 2008, Milstein and Gunanathan reported the alkylation of ammonia with alcohols to form primary amines using ruthenium pincer catalyst.[8] Subsequently, palladium-catalyzed synthesis of primary amines from allylic esters or carbonates[9a] and chiral iridium-catalyzed preparation of primary amines from allylic carbonates[9b] were also described, demonstrating homogeneous catalytic allylic amination with ammonia. Then, Mashima and co-workers disclosed the first platinum-catalyzed direct amination of allylic alcohols with aqueous ammonia.[9c] In addition, the transition-metal catalyzed cross-coupling of aryl halides with ammonia to deliver primary aryl amines was also successfully documented.[3b,c,10–12] Despite constituting progress toward the preparation of primary amines, selective synthesis of primary amines from ammonia still encounters great challenges. These difficulties can be attributed to the following factors. First, most of the routes required transition-metal and ammonia could deactivate the catalyst by forming stable Werner amine complexes. Second, the product primary amines are more nucleophilic than ammonia and cause problematic overreactions, giving mixtures of products. Hence, developing a metal-free, mild, and easy operating method for the selective synthesis of primary amines directly from aqueous ammonia is still highly desirable.*ortho*-Hydroxybenzylamines are emerging as unique building blocks for the construction of natural products and many pharmacologically active compounds.[13] In addition, enantiopure *ortho*-hydroxybenzylamines are a vital class of chiral ligands for transition-metal catalyzed processes[14] and have been used as powerful chiral auxiliaries in the enantioselective synthesis of natural alkaloids.[15] Consequently, a series of strategies for the synthesis of *ortho*-hydroxybenzylamine derivatives have been developed.[15c,16]

Recently, we reported base-induced desulfonylation of 2-(1-tosylalkyl)phenols to generate *o*-Quinone methides (*o*-QMs) and the reaction of *o*-QMs with sulfur ylides to afford *trans*-2, 3-dihydrobenzofurans.[17] Considering aqueous ammonia could serve as base, we envisaged that 2-(1-tosylalkyl)phenols could desulfonylate to deliver *o*-QMs in the presence of aqueous ammonia. On the other hand, aqueous ammonia could also serve as nucleophile. Thus, aqueous ammonia could rapidly undergo Michael addition with the *o*-QMs generated in situ to allow construction of *ortho*-hydroxybenzylamine derivatives. Moreover,

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we speculated that the intramolecular hydrogen bonding between the hydroxy and amino group of *ortho*-hydroxybenzylamines might reduce their nucleophilicity and inhibit further amination. So, the selectivity for formation of primary amines can be improved. Herein, we described a metal-free and concise method for the selective synthesis of primary amines directly from 2-(1-tosylalkyl)-phenols with aqueous ammonia under mild conditions (Scheme 1).

Initial investigation focused on identifying optimal conditions for the direct amination of 2-(1-tosyl-alkyl)phenol **1a** with aqueous ammonia, utilizing 10 equiv of 28% aqueous ammonia and THF as solvent in ambient temperature (Table 1). To our delight, the reaction occurred smoothly to provide the desired product primary amine **2a** in good yield with long reaction time (entry 1). Increasing the reaction temperature, the rate of reaction was accelerated and the yield was further improved to 87% (entry 2). Further evaluation of solvents revealed that the transformation was extraordinarily sensitive to the reaction medium. In dioxane and DMF, **2a** was obtained in good yields (entries 3–4). However, CH_2Cl_2 had a negative effect in terms of the yield (entry 5). Additionally, hexane and Et_2O displayed moderate reactivity (entries 6–7). Interestingly, the reaction also performed well in the poorly water-soluble solvent toluene (entry 8). Thus, the optimal conditions for this reaction were established: using THF as the solvent to perform the reaction at 40 °C.

With the aforementioned conditions, we next sought to define the substrate generality of the present reaction system (Table 2). In general, the reaction conducted smoothly, providing the desired primary amines in good yields and excellent selectivities. For aryl substituents R^1, electronic property had slight influence on the yield and a little lower yield was obtained with the electron-withdrawing groups (entries 1–7). For instance, the reaction gave the target product **2a** and **2g** in 87% and 70% yields, respectively. Notably, alkyl substituted substrates were also suitable reaction partners and the transformation performed well with good yields (entries 8–10). Moreover, the substituents of the phenol did not prohibit the reaction (entries 11–12).

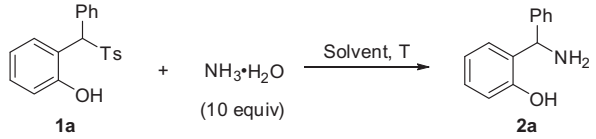
Subsequently, a preliminary study on the asymmetric synthesis of primary amine was also tried. Using cinchona-based thiourea as organocatalyst,[18] moderate 33% ee of enantio-selectivity and 50% yield were obtained (Scheme 2).

To further evaluate the practical utility, the amination of 2-(phenyl(tosyl)-methyl)-phenol **1a** was carried out on gram scale, and the desired product was furnished with 89% yield (Scheme 3).

Given the operational simplicity and broad generality of this direct amination protocol, we explored to demonstrate the utility of this new strategy for the production of biologically active molecules. In the presence of CDI, *ortho*-hydroxybenzylamine product **2a** could be conveniently transformed to benzoxazinone,[19] which is an essential scaffold in numerous important pharmaceutical compounds, in 71% yield according to the known literature method (Scheme 4).[20]

In summary, we have developed a metal-free and concise method for the selective synthesis of primary amines directly from 2-(1-tosylalkyl)phenols with aqueous ammonia under mild conditions in good yields. Moreover, *ortho*-hydroxybenzylamines could be conveniently converted to benzoxazinones. The enantioselective amination with aqueous ammonia has encountered great challenges possibly owing to the small size of ammonia molecule. The asymmetric version of this reaction is in progress in our laboratory.

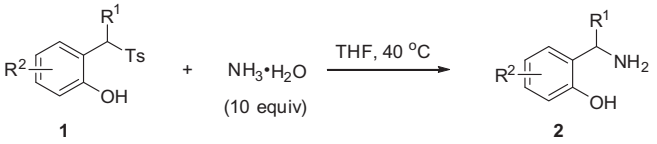
Table 1
Optimization for the reaction of 2-(phenyl(tosyl)-methyl)-phenol **1a** with aqueous ammonia[a]



Entry	Solvent	Temperature	Time (h)	Yield[b] (%)
1	THF	rt	64	75
2	THF	40 °C	16	87
3	Dioxane	40 °C	16	82
4	DMF	40 °C	16	81
5	CH_2Cl_2	40 °C	16	21
6	Hexane	40 °C	16	47
7	Et_2O	40 °C	16	52
8	Toluene	40 °C	16	85

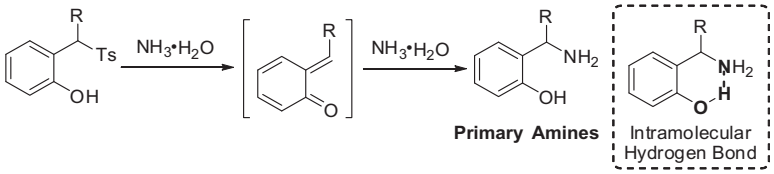
[a] **1a** (0.50 mmol), 28% aqueous ammonia (5.0 mmol), solvent (5.0 mL).
[b] Isolated yields.

Table 2
Scope for the reaction of 2-(1-tosylalkyl)phenols **1** with aqueous ammonia[a]



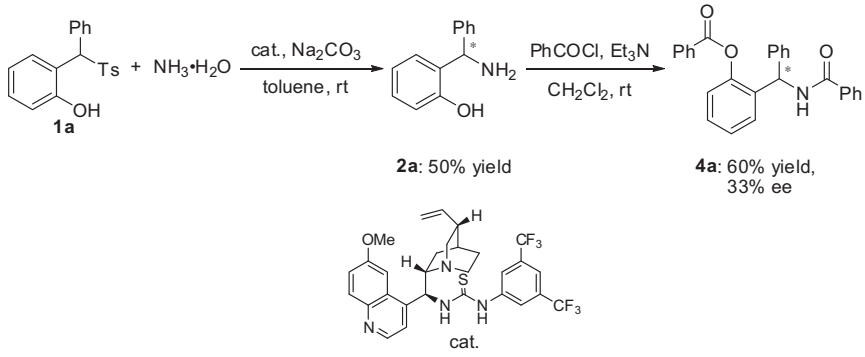
Entry	R^1	R^2	Yield[b] (%)
1	Ph	H	87 (**2a**)
2	2-MeC_6H_4	H	88 (**2b**)
3	3-MeC_6H_4	H	85 (**2c**)
4	4-MeC_6H_4	H	83 (**2d**)
5	4-$MeOC_6H_4$	H	81 (**2e**)
6	4-FC_6H_4	H	72 (**2f**)
7	4-$CF_3C_6H_4$	H	70 (**2g**)
8	Me	H	74 (**2h**)
9	Et	H	87 (**2i**)
10	Bu	H	80 (**2j**)
11	Ph	5-Br	73 (**2k**)
12	Ph	5-OMe	85 (**2l**)

[a] **1** (0.50 mmol), 28% aqueous ammonia (5.0 mmol), THF (5.0 mL), 40 °C, 16–48 h.
[b] Isolated yields.

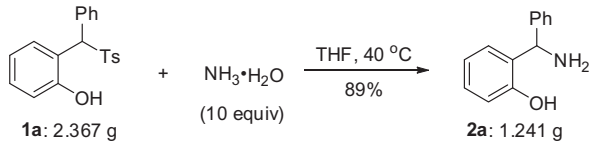


- Aqueous ammonia serves as both base and nitrogen source
- Intramolecular hydrogen bonding between amino and hydroxy group inhibits further amination, improving the selectivity.

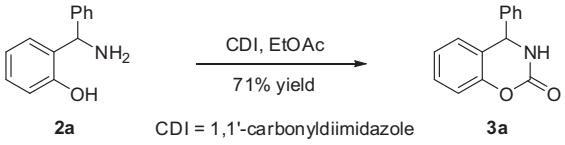
Scheme 1. New strategy for direct synthesis of primary amines from aqueous ammonia.



Scheme 2. Enantioselective synthesis of primary amine **2a**.



Scheme 3. Scale-up of model substrate.



Scheme 4. Synthesis of benzoxazinone **3a**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.078.

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