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A mild and catalyst-free aromatization using dihydroxylcyclohexanone derivatives as phenyl sources: a new approach to anilines

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ABSTRACT

A new and efficient protocol for the preparation of N-substituted anilines via an aromatization reaction was developed. 3,5-Dihydroxylcyclohexanone derivatives were used as the sources of the phenyl group and reacted smoothly with primary or secondary amines under mild conditions in the absence of metal catalyst and strong base. A variety of N-substituted anilines were prepared by this method with excellent yields up to 99%. The results indicate that this reaction begins with a nucleophilic addition.

N-substituted amines are important intermediates for the synthesis of a large number of biologically active natural products, medicines, agrochemicals, and other functional chemicals.[1] The Ullmann-type coupling between amines and substituted arenes is the dominant preparation mean. Palladium catalysis has been generally used for this carbon–nitrogen bond construction.[2] Copper,[3] iron,[4] cadmium,[5] and manganese[6] were also applied. For active substrates, strong bases could be utilized as catalysts.[7] Besides aryl halides, some alternatives such as anilines,[8] aryl sulfonates,[9] aryl carbamates,[10] aryl trimethoxysilanes,[11] arylboronic acids,[12] arylboronates,[13] diphenyliodonium bromides,[14] and some aryl metallics[15] have been explored in the amination with amines. However, these methods suffer from some disadvantages such as the use of metal or strong base as catalysts, high reaction temperature, long reaction time, and low selectivity. Very little attention has been focused on the preparation of N-substituted aromatic amines by means of aromatization of enamines derived from the condensation of cyclohexanone[16] or cyclohexane-1,4-dione[17] with amines. Nevertheless, this procedure inevitably requires stoichiometric amount of metal salts[16a,c] or catalytic amount of Pd/C with toxic nitrobenzene as oxidizer.[16d] In all of the aromatization methods reported, *N*-phenylpiperidine, for example, was obtained in a yield of around 85%.

Asymmetrical hydroxylation of cyclohexanone with nitrosobenzene catalyzed by organocatalysts such as proline is a well-known reaction.[18] We have attempted to utilize this reaction to asymmetrically introduce a hydroxyl group to the 2-positon of (*cis*)-3,5-di(*tert*-butyldimethylsiloxy)cyclohexanone (**4**) catalyzed by L-proline to prepare compound **6**, an intermediate designed for the preparation of lactone moiety (**8**) of statin drugs (Scheme 1). But the results were disappointing. The desired product (**6**) was isolated with a very poor yield of only 16% after reacting at room temperature for 2 days. To our surprise, the yield was even worse (9%) when the reaction was prolonged to seven days. A more soluble derivative 4-*tert*-butyldimethylsiloxy-L-proline (**5**) was used as the organocatalyst and the reaction was slightly faster, however, the yield was still too low (9% yield based on **4**) after 2 days. Despite the low yields obtained, a large amount of *N*-phenylated by-product *N*-phenyl-4-*tert*-butyldimethylsiloxy-L-proline (**7g**, 70% yield based on **5**) was acquired.

So we stopped our attempt to prepare **8** and turned our interest on the reason why **7g** was obtained in such a high yield. Since nitrosobenzene is the only substrate containing the phenyl group in this reaction mixture, nitrosobenzene was stirred with compound **5** in dimethylsulfoxide (DMSO) for 2 days but no *N*-phenylated product was detected. Nevertheless, **4** could react with **5** to afford **7g** with a high yield of 90% based on **5** consumed (60% conversion), though the reaction was very slow (Scheme 2). These results indicate that the phenyl group is derived from cyclohexanone skeleton. The reason why prolonged time gave less desired product but more **7g** might be that the dehydration can be facilitated by the hydroxyl group,[18] that is, in the presence of nitrosobenzene, the expected product 2-hydroxylcyclohexnaone derivative **6** is easier to aromatize.

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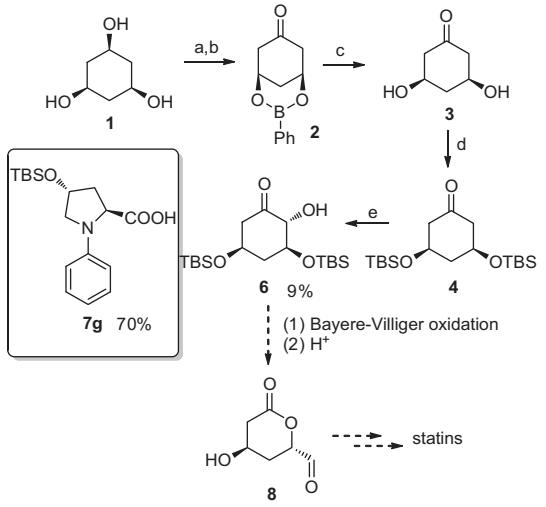
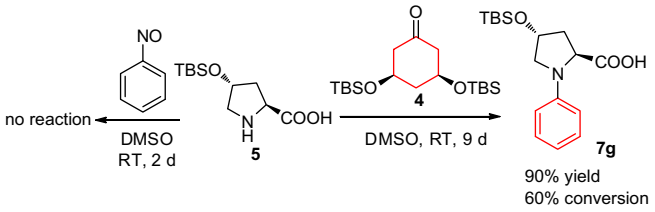


Scheme 1. Unexpected aromatization of **4** observed in the attempt to prepare chiral lactone moiety of statins. Reagents and conditions: (a) phenylboronic acid, toluene, reflux, 5 h, >99%; (b) PCC@Al_2O_3, NaOAc, 4A molecule sieve, CH_2Cl_2, rt, 5 h, 85%; (c) pinacol, THF, $BF_3{\cdot}Et_2O$, rt, 24 h, >99%; (d) TBSCl, imidazole, DMF, RT, 30 min, 99%; (e) 4-*tert*-butyldimethylsiloxy-L-proline (**5**), nitrosobenzene, DMSO, RT, 2 d.



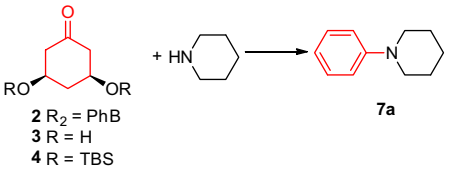
Scheme 2. Aromatization of compound **4** with **5**.

These results directed us to explore a new aromatization reaction to prepare anilines under mild conditions in the absence of any metal catalyst or strong base. Since **4** is relatively stable in comparison with its two precursors 3-phenyl-2,4-dioxa-3-borabicyclo[3.3.1]nonan-7-one (**2**) and 3,5-dihydroxylcyclohexanone (**3**), we believed that the aromatization might be realized more efficiently by using more active 3,5-dihydroxylcyclohexanone derivatives.

Piperidine was used for the model aromatization to optimize the reaction conditions. The results listed in Table 1 indicate that compound **2** has the highest reactivity. When no desiccant was used, the yield was 76% (Table 1, entry 1). Some commonly used inorganic desiccants such as calcium chloride (Table 1, entry 2), magnesium sulfate (Table 1, entry 3), and sodium sulfate (Table 1, entry 4) were applied to absorb the water formed in the reaction, but the yields were only promoted slightly. However, when 4A molecular sieves were used, the yields were achieved almost quantitatively. Both polar and nonpolar solvents gave similar results (Table 1, entries 5–10). 3,5-Dihydroxylcyclohexanone (**3**) exhibits a much lower reactivity, only 12% yield was obtained even reacting under reflux for 24 h in dichloromethane (Table 1, entry 11). The yield was still too low when the reaction was performed in a polar solvent DMSO (Table 1, entry 12). The reaction were extremely slow when 3,5-di(*tert*-butyldimethylsiloxy)cyclohexanone (**4**) were used as the source of the phenyl group (Table 1, entries 13 and 14). The reason might be assigned to the high stability of siloxane in neutral and basic environments.

Based on the results achieved above, compound **2** was used for the following experiments.[19] To investigate the scope of this

Table 1
Model aromatization with piperidine[a]



2 R_2 = PhB
3 R = H
4 R = TBS

Entry	Ketone	Desiccant	Solvent	*t* (°C)	*t* (h)	Yield [b] (%)
1	**2**	None	DCM	Reflux	8	76
2	**2**	$CaCl_2$	DCM	rt	8	81
3	**2**	$MgSO_4$	DCM	rt	8	82
4	**2**	Na_2SO_4	DCM	rt	8	78
5	**2**	4A MS	DCM	rt	6	99
6	**2**	4A MS	PhH	rt	6	99
7	**2**	4A MS	PhH	Reflux	2	99
8	**2**	4A MS	DMF	rt	6	99
9	**2**	4A MS	DMSO	rt	6	99
10	**2**	4A MS	MeCN	rt	6	96
11	**3**	4A MS	DCM	Reflux	24	12
12	**3**	4A MS	DMSO	rt	24	15
13	**4**	4A MS	DMSO	rt	24	Trace
14	**4**	4A MS	DMSO	80	48	35

[a] Reaction conditions: ketone (0.5 mmol), piperidine (0.6 mmol), solvent (8 mL), 4A MS (4 g) or other desiccants (1 g), rt. DCM = dichloromethane, PhH = benzene.
[b] Isolated yields.

aromatization, a variety of secondary amines were applied and the results are listed in Table 2. It can be seen that strong nucleophiles like piperidine, morpholine, diethylamine, and dipropylamine gave corresponding products **7a–d** with excellent yields (Table 2, entries 1–4). However, steric hindrance affects the reaction dramatically. Compared to dipropylamine, dibutylamine showed lower reactivity (Table 2, entry 5). When diisopropylamine was used, only trace product **7k** was detected even reacting under reflux for 24 h (Table 2, entry 11). Compound **5** reacted faster with **2** (Table 2, entry 7) than **4** (Scheme 2) and gave **7g** with higher yield but lower chemoselectivity. The reason might be that the acidic carboxyl facilitates the conversion but, at the same time, accelerates the dehydration of **2** to yield 5-hydroxycyclohex-2-enone, which was detected in the final reaction mixture. To avoid the dehydration side reaction, L-proline methyl ester was used and the result shows that its selectivity is higher than L-proline though the reactivity is lower (Table 2, entries 8 and 9). *N*-methylaniline exhibited reduced reactivity and afforded *N*-methyldiphenylamine **7j** in moderate yield (Table 2, entry 10). Furthermore, diphenylamine shows no reactivity in this reaction (Table 2, entry 12).

Compared to secondary amines, primary amines usually have both less steric hindrance and lower nucleophilicity, but the two factors have opposite influence on nucleophilic reactions. So a variety of primary amines were then explored. The reaction was found to be very smooth and afforded corresponding monophenylated amines with excellent yields (Table 3). Compared to piperidine (Table 2, entry 1), cyclohexanamine reacted obviously faster and afforded the desired product *N*-cyclohexylaniline (**9a**) in quantitative yield (Table 3, entry 1). So we can figure out that steric hindrance is the dominant influence factor on this reaction. This conclusion is also supported by the following facts. Butylamine reacted faster than dibutyl amine at the same reaction conditions, and the yield of *N*-butylaniline (**9b**, 99%, Table 3, entry 2) was much higher than that of *N*,*N*-dibutyl aniline (**7e**, 78%, Table 2, entry 5). The ratio of compound **2** to butylamine was elevated to 3:1, but the yield had almost no change though the reaction was a little faster. Benzylamine and furfurylamine also reacted smoothly with **2** and afforded *N*-benzylaniline (**9c**) and *N*-(furan-2-ylmethyl)aniline