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Conjugated Ketone as Catalyst in Alcohol Amination Reactions under Transition-Metal and Hetero-atom Free Conditions

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Here, we show the results of molecular-defined conjugated ketone catalyzed alcohol amination reaction. Under the optimized reaction conditions, the yields to the desired products reached 98%. Reaction mechanism and kinetic
10 **study supposed that carbonyl-hydroxyl groups are the catalytically active sites, and the transfer-hydrogenation reactions are progressed via the recycling of carbonyl and hydroxyl groups. The catalytic process shows promise for efficient and economic route for alcohol amination reactions.**

15 Alcohol is one of the best established reactants in chemistry. Normally the catalytic activation of alcohol is realized with two different mechanisms.[1] The first one is the activation of alcohol with the addition of acid or base as catalyst to generate electrophilic or nucleophilic species. Alternatively, alcohol can
20 be activated in the presence of a dehydrogenative catalyst. In this way, carbonyl compound will be generated. The carbonyl group can further react with other reactant, typically, amine derivatives, to form imine via dehydration. Ideally the hydride adsorbed onto the catalyst can be transferred to imine again and N-alkyl amine
25 can be synthesized. In the whole process, the sole byproduct is water and the whole process is processed via a transfer-hydrogenation reaction mechanism.

In order to realize these transformations, the presence of transition-metal catalysts is normally essential. In the alcohol
30 amination reactions, a series of homogeneous or heterogeneous transition-metal catalysts such as ruthenium[2], iridium[3], palladium[4], rhodium[5], platinum[6], gold[7], Re[8], silver[9], nickel[10], manganese[11], copper[12] and iron[13] are developed and excellent results are obtained. Recently, boron, aldehyde and carbon based
35 catalysts have been shown to be active catalysts in the transfer-hydrogenation reactions. For example, the catalytic reduction of imine, nitrile, olefin, carbon dioxide and other compounds has been reported using boron complexes as catalysts via the formation of borohydride as the intermediate[14]. Aldehyde
40 molecules have been shown active catalysts in alcohol amination reactions[15]. In addition, carbon material can be perfect catalyst in the catalytic reduction of nitro compounds with hydrazine as the reducing agent, and in the alcohol amination reactions[16].

Based on the extensive results of the transfer hydrogenation
45 reactions and alcohol amination reactions, it can be concluded that the key steps are the dehydrogenation of alcohol to generate carbonyl group and the re-addition of the hydride to the

unsaturated imine bond. In fact it is the recycling of hydride between carbonyl and hydroxyl groups. It inspires us that
50 possibly we can perform the transfer-hydrogenation reaction with ketone as the catalyst. The versatile structure of ketone derivatives gives us great opportunity to tune the catalytic activity. After screening a series of ketone derivatives with different structures, the alcohol amination reactions are realized
55 with high efficiency catalyzed by a simple xanthen-9-one organocatalyst (Scheme 1). N-alkyl amines and alcohols can be synthesized with up to 98% isolated yields via alcohol amination. Reaction mechanism and kinetic study prove the recycling of ketone and hydroxyl groups during the catalytic reaction, i.e. the
60 hydride is first transferred from alcohol to the ketone group of the catalyst, then the hydride is transferred to the desired product and the ketone group is re-generated. The detailed results and discussions are given below.
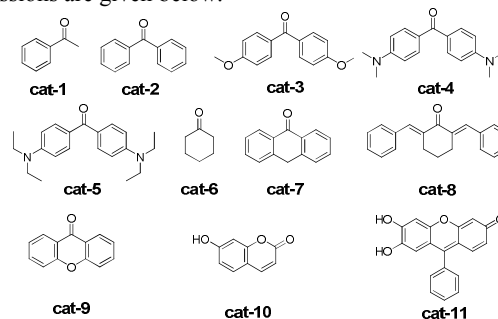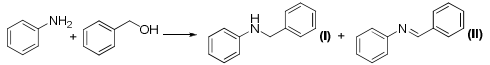

65 **Scheme 1.** Ketone derivatives screened in the work.

The catalytic activity of different ketones in transfer-hydrogenation reactions was explored with aniline and benzyl alcohol as starting materials to synthesize N-benzyl aniline (Table 1). As the typical base and solvent, KOH and toluene were
70 employed. Clearly catalysts **cat-1** to **cat-5** exhibited nice catalytic performance (Entries 1-5). By applying **cat-1** as catalyst, the conversion of aniline was 63% and the yield of N-benzyl aniline was 35%. If **cat-2** was used as the catalyst, the conversion of aniline and the selectivity to N-benzyl aniline can be improved
75 significantly, which resulted in 94% aniline conversion and 80% N-benzyl aniline yield. The incorporation of substituents, such as methoxy, dimethylamino and diethylamino groups, onto the aromatic ring influences the reactivity remarkably. The conversions of aniline were 47-55% with 31-44% N-benzyl
80 aniline yields. If **cat-6** was used as catalyst, it can be seen that 54% aniline conversion and 49% N-benzyl aniline yield were

obtained but almost no reaction occurred if **cat-7** was applied (Entries 6-7). Relatively good results were also obtained if **cat-8** was employed, which conversion was 95% and the yield of N-benzyl aniline was 80% (Entry 8). Noteworthy excellent results were obtained if **cat-9** was used as the catalyst, which conversion was 99% with 96% N-benzyl aniline yield (Entry 9). Then poor results were obtained if **cat-10** and **cat-11** were used as catalysts (Entries 10-11), which mean that the formation of fused ring compound is unfavorable to the transfer-hydrogenation reactions. Following, the influence of base was studied (Entries 12-17). Clearly, the applying of strong base is helpful for the transfer-hydrogenation reactions. Lower conversion and selectivity were obtained if NaOH, K_2CO_3, Na_2CO_3 and CaO were employed. Poor results were obtained if the reaction was performed under base free conditions, the conversion of aniline was <1%. Then the solvent variation was explored. Commonly organic solvents including xylene, mesitylene, dioxane, acetonitrile, tetrahydrofuran and octane were applied in the transfer-hydrogenation reactions (Entries 18-22). Clearly, the properties of the solvents influenced the transfer-hydrogenation reaction remarkably and nonpolar solvents are helpful to the reaction. It should be mentioned that although 99% aniline conversion was achieved when tetrahydrofuran was used as solvent almost no desired product was obtained. The major products were 1-phenylpyrrolidine and 1-phenyl-pyrrole. In addition, relatively good results were obtained if 1.2 equiv., of benzyl alcohol was employed (Entries 23). Only 11% desired product was obtained if KOH itself was used as catalyst (Entry 24). Therefore, the ketone should be the main catalyst.

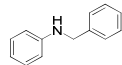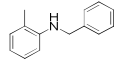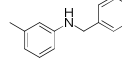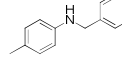**Table 1.** Catalysts screening and reaction conditions optimization.[a]
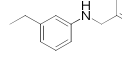
Entry	Catal.	Bases	Solvents	Conv./%[b]	Y./%[b]
1	Cat-1	KOH	PhMe	63	35
2	Cat-2	KOH	PhMe	94	80
3	Cat-3	KOH	PhMe	53	31
4	Cat-4	KOH	PhMe	47	33
5	Cat-5	KOH	PhMe	55	44
6	Cat-6	KOH	PhMe	54	49
7	Cat-7	KOH	PhMe	4	<1
8	Cat-8	KOH	PhMe	95	80
9	**Cat-9**	**KOH**	**PhMe**	**99**	**96 (95^c)**
10	Cat-10	KOH	PhMe	<1	----
11	Cat-11	KOH	PhMe	<1	----
12	Cat-9	NaOH	PhMe	33	19
13	Cat-9	K_2CO_3	PhMe	<1	----
14	Cat-9	Na_2CO_3	PhMe	<1	----
15	Cat-9	CaO	PhMe	8	<1
16	Cat-9	----	PhMe	<1	----
17	Cat-9	KOH	Xylene	59	50
18	Cat-9	KOH	Mesitylene	22	15
19	Cat-9	KOH	Dioxane	7	5
20	Cat-9	KOH	CH_3CN	7	<1
21	Cat-9	KOH	THF	99	<1^d
22	Cat-9	KOH	Octane	35	27
23^e	Cat-9	KOH	PhMe	90	85
24^f	----	KOH	PhMe	13	11
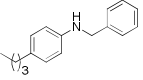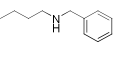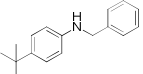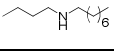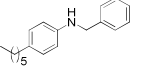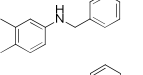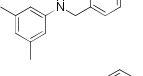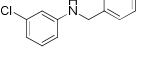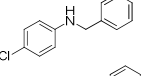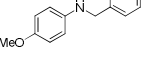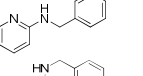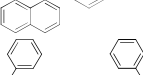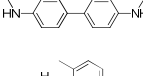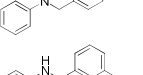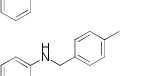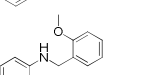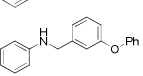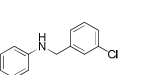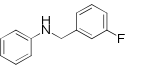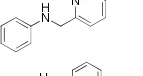
[a] Reaction conditions: 1 mmol aniline, 1.5 mmol benzyl alcohol, 50 mg catalyst, 0.5 mmol KOH, 2 mL solvent, Ar, 150 °C, 4 h. [b] conversion of and yield determined by GC-FID with biphenyl as an external standard material. [c] isolated yield. [d] the products were 1-phenylpyrrolidine and 1-phenyl-pyrrole. [e] 1.2 mmol benzyl alcohol was used.

Next, this optimized reaction condition was applied in the alcohol amination reactions with different amine and alcohol using **cat-9** as catalyst (Table 2). Various structurally diverse amines, regardless of the presence of electron-withdrawing or electron-donating functional groups, were monoalkylated with benzyl alcohol to yield the corresponding secondary amines in excellent yields. For example, N-benzyl aniline was synthesized in 95% yield in 4 h (entry 1). The substituents at different positions on the aniline significantly affected the reaction rate. For example, a lower yield was obtained when *o*-methylaniline was used as a substrate compared with *p*-methylaniline and *m*-methylaniline (entries 2-4). Excellent results were also obtained if other alkyl substituents, i.e., ethyl, butyl, tert-butyl, hexyl and di-methyl groups, were involved (entries 5-10). The yields of the desired products were 84-98%. The reaction tolerated the presence of chloro and methoxyl groups (entries 11-13), and 80-98% yields of the desired products were observed when *m*- or *p*-chloro or *m*-MeO-anilines were used as starting materials. The reactions of 2-aminopyridine, naphthalen-1-amine and benzidine with benzyl alcohol resulted in 95-98% yields (entries 14-16). The reaction also proceeded successfully with other structurally and electronically diverse alcohols. Benzyl alcohol with moderately activating groups reacted smoothly and furnished excellent yields of the respective mono-N-alkylated anilines (entries 17-21). Alcohols with a chlorine or fluoro substituent reacted with aniline to afford the corresponding products with 100% conversion with up to 95% yields (entries 22-23). The **cat-9** catalyst also exhibits promise for direct coupling of aniline with simple heteroaromatic alcohols under similar reaction conditions in excellent yields (entries 24-25). *p*-Methylthiobenzyl alcohol was converted to the respective secondary amine in 95% yield (entry 26). To our delight, aliphatic primary amine and aliphatic primary alcohol, i.e., butyl amine, butanol and octano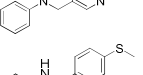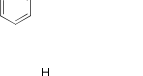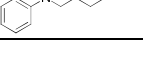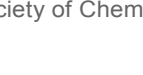l can also be used in the ketone molecule catalyzed transfer-hydrogenation reactions. Typically the starting materials can be converted efficiently but a mixture of the N-alkyl amine and N-alkyl imine products were obtained (entries 27-29). These results suggest a nice generality of the molecular-defined ketone catalyst in the alcohol amination reactions with different amine and alcohols as starting materials.

Table 2. Scope and limitation test of the alcohol amination reactions.[a]

$$R^1NH_2 + R^2CH_2OH \longrightarrow R^1NHCH_2R^2$$

	a1	**b1**	**c1**		
Entry	R^1	R^2	Product	t/h	Y./%[b]
1	Ph	Ph		4	95
2	*o*-Me-Ph	Ph		8	61
3	*m*-Me-Ph	Ph		4	97
4	*p*-Me-Ph	Ph		4	93
5	*m*-Et-Ph	Ph		8	84

Entry	R1	R2	Product	Time	Yield
6	p-Bu-Ph	Ph		8	85
7	p-tert-Bu-Ph	Ph-		8	92
8	p-Hexyl-Ph	Ph		8	88
9	3,4-di-Me-Ph	Ph		8	98
10	3,5-di-Me-Ph	Ph		8	86
11	m-Cl-Ph	Ph		8	98
12	p-Cl-Ph	Ph		4	92
13	p-MeO-Ph	Ph		4	80
14	2-Py	Ph		8	98
15	1-Naphthyl	Ph		4	95
16	Benzidine	Ph		8	87
17	Ph	o-Me-Ph		4	96
18	Ph	m-Me-Ph		4	96
19	Ph	p-Me-Ph		4	84
20	Ph	o-MeO-Ph		8	83
21	Ph	m-PhO-Ph		8	97
22	Ph	m-Cl-Ph		8	95
23	Ph	m-F-Ph		8	64
24	Ph	2-Py		8	98
25	Ph	3-Py		8	76
26	Ph	p-MeS-Ph		8	95
27	Ph	Butyl		24	53[c](65/15[d])
28	Bu-	Ph-		24	77[c](20/73[d])
29	Bu-	Octyl-		24	78[c](0/99[d])

[a] Reaction conditions: 1 mmol amine, 1.5 mmol alcohol, 50 mg cat-9, 0.5 mmol KOH, 2 mL toluene, Ar, 150 ºC, 4-24 h. [b] isolated yield. [c] Conversions of the amines determined by GC-MS. [d] Selectivities of N-alkyl amine and N-alkyl imine determined by GC-MS.

In order to explain the catalytic activity variation of different catalysts, the transformations of the catalysts during catalytic reaction were explored with **cat-2**, **cat-3** and **cat-9** as the model catalysts. By analyzing the reaction mixtures after reactions (Table 1), it can be seen that a part of the catalysts were transferred to the corresponding alcohols. These results showed that catalytic cycle might be between carbonyl and hydroxyl groups, and the hydrogenation ability of the ketone and dehydrogenation ability of the corresponding alcohol should be responsible for the catalytic activity variation. In order to clarify the reaction mechanism and catalytic activity variation of different catalysts, following control reactions were performed under the given reaction conditions in Table 1, i.e., **(a)** reaction of **cat-2** with benzyl alcohol, **(b)** reaction oif **cat-3** with benzyl alcohol, **(c)** reaction of **cat-9** with benzyl alcohol, **(d)** reaction of **cat-2-OH** with benzaldehyde/aniline, **(e)** reaction of **cat-3-OH** with benzaldehyde/aniline and **(f)** reaction of **cat-9-OH** with benzaldehyde/aniline (Scheme 2). After reaction, a mixture of ketones, i.e., **cat-2, 3** and **9**, and the corresponding alcohols were formed. The ratios of ketones to the alcohols were 7.5 : 92.5, 28 : 72 and 98 : 2 in reactions **(a)** to **(c)**. The results suggested that **cat-2** could be easily hydrogenated to **cat-2-OH** but **cat-9** was different to be reduced under the same reaction conditions. About **cat-3**, it can be smoothly reduced to **cat-3-OH**, too. During these transformations, benzyl alcohol was oxidized to benzaldehyde. Interestingly, the ratios of the ketones to the corresponding alcohols were 41 : 59, <<1 : 99 and >>100 : 1 in reactions **(d)** to **(f)**. These results showed that the hydride can be efficiently transferred from **cat-9-OH** to the imine intermediate (benzaldehyde+aniline) to generate N-benzyl aniline while the dehydrogenation of **cat-3-OH** was quite difficult. About **cat-2-OH**, its dehydrogenation ability was moderate. It should be interesting if taking the results of N-alkyl aniline synthesis with **cat-2, 3** and **9** as catalysts into consideration together. The conversions of aniline were 94%, 53% and 99% with 85%, 58% and 97% N-benzyl aniline selectivities (Table 1, entries 2,3 and 9). The relatively good results with **cat-2** as catalyst might be attributed to the good recycling between **cat-2** and **cat-2-OH**. For the excellent catalytic activity of **cat-9**, it can be explained by the extremely good performance of the transferring of hydrogen atom from **cat-9-OH** to the imine intermediate so it can promote the progress of the reaction efficiently. About catalyst **cat-3**, although it is active for the activation of benzyl alcohol to generate benzaldehyde, it is less active for the transfer-hydrogenation of imine intermediate from **cat-3-OH** to form the desired product, which might be responsible for the lower activity. Based on the above discussion, it can be concluded partially that the crucial step in the catalyst recycling might be the transferring of hydride to the imine intermediate from **cat-OH** and a reaction mechanism was proposed as Scheme 2 (g).

Scheme 2. Reaction mechanism exploration. The results were determined by GC-MS with external standard method.

In conclusion, an efficient molecular-defined organocatalyst was developed for the transfer-hydrogenation reactions including alcohol amination and carbonyl compound reduction. The ketone and alcohol groups inside the catalyst are the active sites of the catalyst. To the best of our knowledge, this is the first time to show that ketone with a specific structure can be an active catalyst for transfer-hydrogenation reactions. It should be helpful for us to understand the transfer-hydrogenation reaction and also provides an efficient methodology for such transformations.

Notes and references

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†Electronic Supplementary Information (ESI) available: The details about the characterization of isolated compounds. See DOI: 10.1039/b000000x/

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Conjugated Ketone as Catalyst in Alcohol Amination Reactions under Transition-Metal and Hetero-atom Free Conditions

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Molecular-defined conjugated ketone can be an active catalyst for the alcohol amination reactions with up to 98% isolated yields to the desired products.