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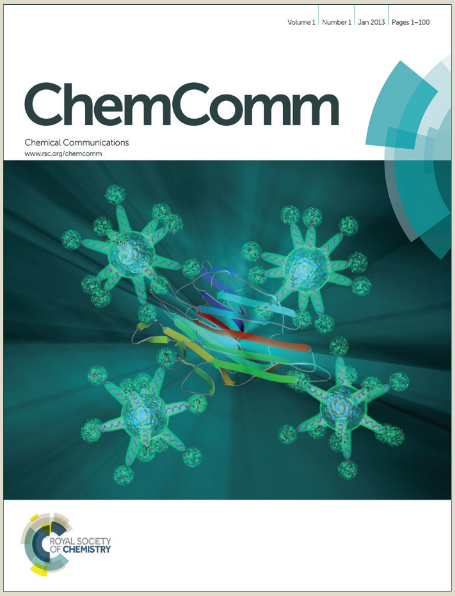

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A highly efficient thiazolylidene catalyzed acetoin formation: reaction, tolerance and catalyst recycling

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An efficient acetoin formation from acetaldehyde was achieved under the thiazolylidene catalysis. High yields and TON were achieved. Its sufficient tolerance toward ethanol and moisture renders it a practical key step of the ethanol upgrading process. A new type of solid supported thiazolylidene catalyst was designed to make catalyst recycling achievable.

Acetoin is a popular food flavor and an additive in many dairy products. It is also a valuable building block for value-added molecule construction[1]: especially as the potential key intermediate,[2] through which bulk C4 chemicals (such as butene and butadiol) can be selectively produced from the abundant and renewable bioethanol.[3] Traditionally, acetoin is mainly produced from bacteria by enzyme catalyzed decarboxylation of acetolactic acid or oxidization of butanone.[4] These biochemical synthetic routes usually resulted in low yields and/or high costs, which makes the bulk production of acetoin difficult. Alternatively, as one of the bulk C4 chemicals, acetoin could be chemically synthesized *via* ethanol derivation and upgrading sequence[2,3] - Dehydrogenation/oxidation to acetaldehyde[5] followed by an acetoin condensation.[6] This two-step reaction sequence may bridge the gap between bioethanol and industry C4 chemicals: It not only represents a more economically viable manner, but also represents an environmentally friendly pathway - leading to the decrease in CO_2 emission.[3] Therefore, it is highly desirable to develop an efficient process for the acetoin formation from ethanol.

As early as in 1958, Breslow[6] disclosed the mechanism of *N*-Heterocyclic Carbene (NHC)[7] catalyzed benzoin condensation, which represents an atomically economic and mild C-C bond formation. However, unlike the extensively studied benzoin formation,[6] the aliphatic acyloin formation through NHC catalysis are less explored, [8,9] especially the acetoin formation: These acetoin formations usually are limited in the lab scale due to the high catalyst loadings (usually 5 mol% to 30 mol%). Recently, it has been found that the structural modifications of thiazolylidene NHC could efficiently catalyze the acetoin formation from acetaldehyde under neat conditions.[2,10] In these cases, the catalytic loadings could be lowered down to 1 wt% (or 1 mol%). Herein, we demonstrate that the NHC generated from a commercially available thiazolium salt **1** is able to catalyze the acetoin reaction efficiently [Figure 1]. Excellent yields could be achieved in the acetoin reaction from acetaldehyde even with only 0.045 mol% (0.25 wt%) thiazolium precatalyst loaded. [11] It represents the most efficient one for the acetoin formation from acetaldehyde to our best knowledge. More importantly, this catalytic system is able to tolerate moisture and ethanol impurities, thus it is suitable for a combined process from ethanol to acetoin, which is also demonstrated in this report. In addition, the strategies for the catalyst isolation and recycling are explored.

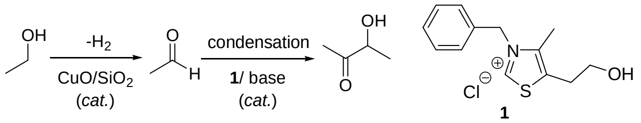
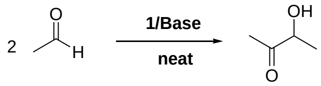


Figure 1. Ethanol upgrading to acetoin *via* the thiazolylidene catalyzed acetoin condensation.

Assuming 1 equiv of NHC catalyst could be generated *in-situ* from 1 equiv of precatalyst **1** in the presence of slightly excess amount of base (1 - 1.5 equiv), and instead of selecting the solvents, we started the reaction condition optimizations by screening of a series of bases under solvent-free conditions [Table 1]. Our initial efforts was based on the previous related reports, in which acetoin could be obtained in good yield up to 68% in the presence of 5 mol% precatalyst **1** and 30 mol% Et_3N in absolute ethanol.[8] However, under the solvent-free condition, when decreasing the amount of precatalyst **1** and Et_3N (or other organic base such as DBU) to 1 mol%, acetoin was formed in less than 50% yield, companied with other side products [entries 1 and 2, Table 1]. In contrast, it was found that the inorganic bases including Na_2CO_3, KOAc, NaOH and K_2CO_3 worked well for this reaction [entries 3-6, Table 1].

To pursue the maximum efficiency of this catalytic reaction, the possibility of decreasing the catalyst loading is also explored [entries 7-10, Table 1]. It was found that in a large scale (43 mL), with 0.1 mol% precatalyst 1 loaded, the reaction was completed at 120 °C in 16 hours to yield 98% acetoin and almost no side product was observed [entry 9, Table 1]. In this acetoin reaction, NHC generated from 1 demonstrated extremely high catalytic activity: Very high turnover number (TON = 490**,** based on product) was achieved. In an even larger scale test (100 ml), with 0.045 mol% precatalyst 1/sodium hydroxide, acetoin yield is 85% (TON = 944) [entry 10, Table 1]. For the first time, such high turnover numbers were observed for the organo-NHC catalyzed acetoin reaction. This high efficiency probably resulted from the neat condition. The reactive NHC catalyst and Breslow intermediate[6] can be trapped by acetaldehydes to generate the desired acetoin in an immediate and almost exclusive manner due to the extreme concentration of the acetaldehyde (Schem S1, SI).

Table 1. Thiazolydiene catalyzed acetoin reaction: reaction condition optimizations.[a]

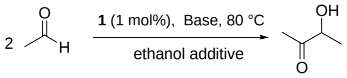


E	Cat. (mol%)	Base (mol%)	Scale (ml)	T (°C)	Time (h)	Y (%)	TON
1	**1** (1)	Et$_3$N (1)	2	80	1	<50[b]	<25
2	**1** (1)	DBU (1)	2	80	1	<50[b]	<25
3	**1** (1)	Na$_2$CO$_3$ (1)	2	80	1	95	47.5
4	**1** (1)	KOAc (1.1)	2	80	1	90	45
5	**1** (1)	NaOH (1)	2	80	0.8	95	47.5
6	**1** (1)	K$_2$CO$_3$ (1)	2	80	1	98	49
7	**1** (0.1)	K$_2$CO$_3$ (0.1)	43	120	5	91	455
8	**1** (0.04)	K$_2$CO$_3$ (0.04)	102	120	16	77[b]	962.5
9	**1** (0.1)	NaOH (0.13)	43	120	16	98	490
10	**1** (0.045)	NaOH (0.06)	100	120	15	85	944

[a] Reaction conditions: a mixture of **1**, base and acetaldehyde was stirred in a sealed tube at the indicated time and temperature. [b] by-products were detected.

In the process of upgrading bioethanol to C4 chemicals, acetaldehyde is usually obtained from ethanol by dehydrogenation/oxidation.[5] As the result, moisture as well as residual ethanol are inevitable in the acetaldehyde feedstock. Herein, the tolerances to ethanol and moisture were tested in this catalytic acetoin formation system. As shown in Table 2, without any pretreatment of reactors and reagents, the existence of ethanol (up to 13 wt%) had little influence on the reaction [entries 1-3, Table 2]. These positive preliminary results encouraged us to apply this catalytic acetoin reaction as the key step for the ethanol upgrading process: ethanol was firstly subjected to the CuO/SiO$_2$(SBA-16)[12] catalyzed dehydrogenation on a fix-bed reaction system, the collected acetaldehyde [4 g acetaldehyde (purity 83% with unreacted ethanol as the major impurity)] was directly used as the feedstock for the acetoin condensation reaction. To our delight, acetaldehyde underwent a 99% conversion exclusively to acetoin under the catalysis of 1 mol% of **1**/dry K$_2$CO$_3$ [entry 4, Table 2].

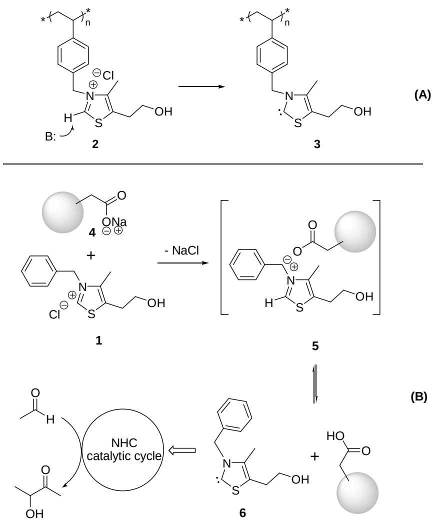
Table 2. Moisture and ethanol tolerances for thiazolydiene catalyzed reaction.[a]



Entry	Base (mol%)	Ethanol (wt%)	Time (min)	Yield (%)
1	K$_2$CO$_3$ (1)	5	50	98
2	K$_2$CO$_3$ (1)	13	50	95
3	NaOH (1)	13	50	95
4[b]	K$_2$CO$_3$ (1)	27	120	99

[a] Reaction conditions: a mixture of as-purchased **1**, base and acetaldehyde was stirred in an air-dried sealed tube at the indicated times and temperature. [b] Raw acetaldehyde synthesized from the ethanol.

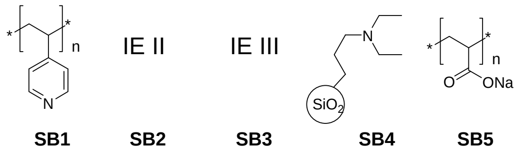
It is well known that immobilization is one of most efficient ways for heterogeneous catalysis and catalyst recycling.[13] However, the catalytic recycling based on supported organo-NHCs are rarely explored.[13i, 14] Herein, we expect to design effective supported system to realize the thiazolydiene NHC catalyst recycling for this acetoin reaction. As shown in Scheme 1A, polystyrene supported precatalyst **2** can be activated with base to form the supported NHC catalyst **3**. Combining the advantageous fact in this catalytic system - the NHC is generated from the *in-situ* deprotonation of the precatalyst **1** by a base, a novel protocol for the NHC catalyst recycling could be proposed with the aid of a solid or supported base. As an example shown as Scheme 1B, when solid sodium carboxylate **4** was used as base, it would attract **1** *via* the electronic interaction to form a solid thiazolium-carboxylate ion pair **5**, which is in equilibrium with the carboxylic acid and NHC **6**. With this design, the precatalyst could be isolated (via **5**) and re-enter the catalytic cycle as NHC **6**.



Scheme 1. Approaches for heterogeneous catalysis and catalyst recycling.

To verify the potential of the above proposed methods, polystyrene supported thiazolium precatalyst **2** [Scheme 1] was prepared (SI) and several solid bases were applied for this acetoin formation [Table 3]. As shown in entry 1, Table 3, the activity of solid precatalyst **2** is lower than precatalyst **1**: with **2**, longer reaction time (4 h with **2** *vs* 1 h with **1**) was necessary to achieve the complete conversion. The recycled solid catalyst **2** gave even much lower reactivity [entry 2], probably due to the low stability of the reactive carbene species **3** [Scheme 1]. In parallel, precatalyst **1** with oven-dried solid bases **SB1**, **SB2** and **SB3** did not give promising results, probably due to the high water content in these commercial solid bases. However, they could give excellent (> 95%) acetoin yields when dry reagents [molecular sieve (MS)] were applied *in-situ* [entries 3-5, Table 3], Interestingly, when applying precatalyst **1** (1 mol%) in combination with bases **SB4** and **SB5 (SI),** excellent acetoin yields (98%) were achieved even without any pretreatment and drying additive [entry 6 and entry 8]. The catalyst could be recycled together with solid bases, although there were different extents of deactivations observed for the recycled catalysts [entries 6-10, Table 3]. These promising results may attribute to the equilibrium between **5** and **6** as we proposed in Scheme 1, which allows the reactive carbene species **6** to go back to the catalytic cycle. In addition, the combination of solid catalyst **2** and solid bases has also been tested for the current reaction [entry 11-15, Table 3]. The combination of **2** with weak solid base **SB5** showed rather low activities [entry 11] even for the first time use. As **2** was used together with stronger solid base **SB4** and **SB3**, good catalytic activities were observed [entry 12 and entry 14] for the first time use. The catalysts were also recyclable, but the activities of recycled catalysts were dropped obviously [entry 13 and entry 15].

Table 3. Acetoin formation with supported catalysts.[a]



E	Precat. (mol%)	Base (mol%)	Temp (°C)	Time (h)	Yield (%)
1	**2** (1)	K_2CO_3(1)	80	4	95
2	**2** (reused)	K_2CO_3(1)	80	4	< 10
3[b]	**1** (1)	SB1 (5)	120	2	95
4[b]	**1** (1)	SB2 (5)	120	2	95
5[b]	**1** (1)	SB3 (5)	120	2	95
6[c]	**1** (1)	SB4 (1)	120	1	98
7[c]	reused		120	2	36
8	**1** (1)	SB5 (1)	120	2	98
9	reused (1st)		120	2	95
10	reused (2nd)		120	2	55[d]
11	**2** (1)	SB5 (1)	120	3	69
12	**2** (1)	SB4(1)	120	24	88
13	reused		120	24	46
14	**2**(1)	SB3 (5)	120	2	83[d]
15	reused		120	2	42[d]

[a]Reaction conditions: a mixture of precatalyst, base and 2 ml acetaldehyde was stirred in a sealed tube. [b] 200mg of ion exchanger resin was used in the presence of 300 mg of 4Å MS. [c] 8 ml acetaldehyde was added. [d] by-products were detected.

Conclusions

In conclusion, a highly efficient and robust acetoin formation from acetaldehyde has been achieved under the catalysis of the thiazolylidene NHC, which was formed *in-situ* by deprotonation of the commercially available thiazolium salt with a base. High yields and selectivities were achieved with extremely low precatalyst loadings (as low to 0.045 mol%). This reaction system is sufficiently tolerant toward ethanol and moisture, rendering it the practical key step of the ethanol to C4 chemicals upgrading process. The possibility of catalyst separations and recycling has been successfully demonstrated by designing the novel heterogeneous NHC catalysts based on precatalyst **1**: The supported NHCs, which were generated by *ad-hoc* deprotonation/immobilization of **1** with a solid base (ion-exchanger), demonstrated great potential as recyclable NHC catalysts for the acetion reaction. To further improve the sustainability of this method, the structural optimizations of above-mentioned heterogeneous catalysts are ongoing in our laboratory.

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details, reaction and synthesis procedures. See DOI: 10.1039/b000000x/

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