

Highly efficient heterogeneous procedure for the conjugate addition of amines to electron deficient alkenes

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The novel efficient procedure has been developed for the conjugate addition of amines to electron deficient alkenes. K₂CO₃ supported on different carriers have been synthesized for the conjugate addition of amines and alkenes. After optimizing the reaction conditions, K₂CO₃/MgO was chosen as the most efficient catalyst for the reactions. The results showed that the catalyst was very efficient for the conjugate addition of amines to electron deficient alkenes with the excellent yields in several minutes. Operational simplicity, without need of any solvent, low cost of the catalyst used, high yields, reusability, excellent chemoselectivity, and applicability to large-scale reactions are the key features of this methodology.

heterogeneity, conjugate addition, chemoselectivity, catalysis, solvent-free

1 Introduction

The formation of carbon-nitrogen bonds by simple addition of amines to double bonds is a focus of increasing interest and widely used in organic synthesis owing to the importance of the resultant β -amino compounds^[1]. These β -amino carbonyl compounds are versatile synthetic intermediates for the synthesis of a variety of biologically important natural products, and antibiotics and are useful in fine chemicals and pharmaceuticals^[2,3]. Compared to the Mannich reaction^[4], Michael addition is a very straightforward approach for the synthesis of substituted amines and their derivatives with 100% atom efficiency and without any byproduct formation^[5]. In general, this type of conjugated addition reaction requires basic conditions or acidic catalysts. A number of alternative procedures have been reported recently using a variety of reagents such as Pd compounds, InCl₃, CeCl₃, Yb(OTf)₃, Bi(NO₃)₃, Bi(OTf)₃, Cu(OAc)₂, LiClO₄, clay, silica gel, SmI₂, FeCl₃, CrCl₃, and SnCl₄^[6–23]. Although some of

these methods are quite useful, many suffer from limitations such as the requirement for a large excess of reagents, long reaction time, harsh reaction conditions and toxic solvents such as acetonitrile or 1,2-dichloroethane. Hence, the development of less expensive, simpler, “greener” catalysts for the reactions is still highly desirable. Recently, K₂CO₃ supported on the carriers were widely used as heterogeneous base catalysts in organic synthesis. Aiming at these advantages, we developed a solvent-free protocol for the conjugate addition of amines to electron deficient alkenes using the catalyst. The results showed that the catalysts were very efficient for the reactions with the good to excellent yields in several minutes.

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2 Experimental

All organic reagents were commercial products with the highest purity available (>98%) and used for the reactions without further purification. MgO, Al₂O₃, CaO, TiO₂, SnO₂, SiO₂, ZrO₂ were commercial products from Shanghai Chemicals Co. and used as the carriers without any treatment.

2.1 Synthesis of catalysts

Here we provide a simple method for the preparation of the K₂CO₃ supported on carriers catalysts by the solid-reaction method. All the carriers were commercially available products and used without any treatment. Certain amount of K₂CO₃ and carriers were mixed together in a mortar and skived for half an hour. After being dried in the oven at 80 °C for 4 h, the solid was calcined at 600 °C for 3 h.

2.2 The conjugate addition of amines to electron deficient alkenes

Typical procedure for the conjugate addition of amines: A mixture of amines (20 mmol), alkenes (24 mmol) and the catalyst (50 mg) was stirred at room temperature for a certain time as shown below. The process of the reaction was monitored by GC analysis. The reaction mixture was extracted with ethyl acetate (2×20 mL) and the combined extract was dried over Na₂SO₄ and evaporated to leave a crude product which was separated by column chromatography using neutral alumina as stationary phase (petroleum ether/ethyl acetate (95 : 5)) and eluent to give the corresponding products.

3 Results and discussion

3.1 The effect of the loading ratio of K₂CO₃/MgO on the reaction

The reaction between dibutylamine and methyl acrylate was used as the model reaction to investigate the effect of the loading ratio of K₂CO₃/MgO (Table 1). The results showed that the K₂CO₃ amount had a key effect on the reaction. The reaction could not be efficiently activated with little K₂CO₃ amount, while there was not enough active sites on the catalyst. When the loading ratio of K₂CO₃/MgO reached 0.7, the reaction went on smoothly with the excellent yield of 98%. Further increasing the amount of K₂CO₃ seemed to be meaningless for the reaction with the yield remaining the same. So the optimal loading ratio of the catalyst was chosen

as 0.7 below.

Table 1 The effect of the loading ratio on the reaction

Entry	Loading ratio ^{a)}	Yield (%) ^{b), c)}
1	0.1	32
2	0.3	43
3	0.5	66
4	0.7	99
5	0.9	94

a) Loading ratio refers to $m(\text{K}_2\text{CO}_3)/m(\text{MgO})$; b) the reaction conditions: dibutylamine (20 mmol), methyl acrylate (24 mmol), catalyst (50 mg), and r.t. (25 °C) for 5 min; c) isolated yield.

3.2 The effect of the different carriers of the catalyst on the reaction

K₂CO₃ supported on different carriers was investigated with the optimal loading ratio of 0.7 (Table 2). The results showed that the carrier also had important effect on the reactions with the good to excellent yield. The carriers with base owned relatively high activities compared with those with acidity such as TiO₂, SnO₂, SiO₂, ZrO₂ owing to the strong interaction between K₂CO₃ and the carriers. K₂CO₃/Al₂O₃ owned high activity for the reaction on the high BET surface of the carrier and the interaction between K₂CO₃ and Al₂O₃, which caused stronger active sites and made them well-dispersed. Here K₂CO₃/MgO offered the highest yield for its additional base from the MgO instinct. K₂CO₃/CaO had the equal activity for its sensitivity to the water and easy change to the hydroxide. So K₂CO₃/MgO was chosen as the catalyst for the reactions below.

Table 2 The effect of carriers on the reaction

Entry	Carrier	Yield (%) ^{a), b)}
1	Al ₂ O ₃	91
2	MgO	94
3	ZnO	90
4	CaO	92
5	ZrO ₂	89
6	TiO ₂	87
7	SnO ₂	86
8	Ac	92
9	SiO ₂	88

a) The reaction conditions: dibutylamine (20 mmol), methyl acrylate (24 mmol), catalyst (50 mg), and r.t. (25 °C) for 5 min; b) isolated yield.

3.3 Catalytic procedure for the conjugate addition

The conjugate additions of various amines with alkenes using K₂CO₃/MgO under solvent-free condition were investigated (Table 3). The results showed that the reac-

tions carried out with K_2CO_3/MgO as heterogeneous catalyst went on smoothly at room temperature under solvent-free conditions within several minutes. The dimethylamine showed extremely high activity for all kinds of electron deficient alkenes with almost complete conversion within 10 min (entries 1, 6, 10, 16). The yields slightly dropped with the carbon atomicity of the amines added because of the steric hinderance (entries 2, 3, 7, 8, 11, 12, 17, 18). Here the catalyst was also efficient for the multi-amino compound such as ethanediamine (entries 4, 15). Both amino groups reacted with the

alkenes yielding over 90% in short time. The primary amines underwent the single substitution reaction under the reaction condition (entries 3, 8, 12, 18). These results indicated the usefulness of the novel catalyst for the reactions and the reaction conditions are mild and not sufficient to cause double substitution reaction. The multi-substitution reaction could also be activated when more alkenes and high temperature were applied, then the double substituted products were obtained with high yields. Ethanolamine and 3-methoxy propylamine also converted to the corresponding products without

Table 3 The conjugate additions of various amines with alkenes

Entry	Amines	Alkenes	Reaction time (min)	Yield (%) ^{a), b)}
1			10	99.2
2			15	97.4
3			10	97.2
4			20	95.5
5			30	93.5
6			10	98.2
7			20	96.5
8			10	96.6
9			35	92.5
10			10	97.2
11			30	95.3
12			15	93.5
13			30	91.5
14			35	90.1
15			40	90.6
16			10	97.1
17			20	94.4
18			15	95.2
19			25	90.5

a) The reaction conditions: amine 20 mmol, alkenes 24 mmol, catalyst 50 mg, r.t. (25°C); b) isolated yield.

destroying the hydroxyl and methoxy groups (entries 5, 9, 13, 14, 19). As for the alkenes, the reactivity was affected by the EWG and the steric hindrance also had the certain effect on the reaction.

3.4 The reuse of the catalyst

One property of the catalyst is the heterogeneous catalytic process. Thus, recovery of the catalyst is very convenient. After reactions, the catalyst was recovered by filtration. The recovered activities were investigated through the reaction of dibutylamine and methyl acrylate carefully (Figure 1). The yield remained unchanged even after the catalyst had been recycled for six times.

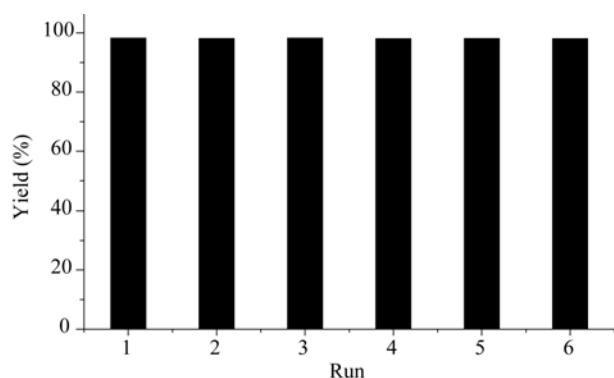
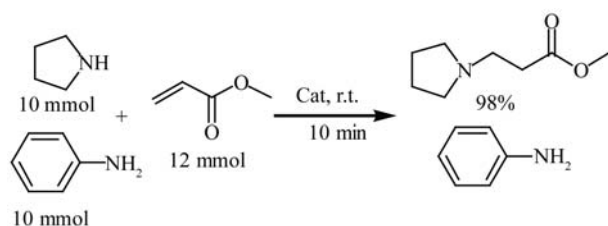


Figure 1 The reuse of the catalyst K_2CO_3/MgO .

3.5 The chemoselectivity of the catalyst

It is noteworthy that aromatic amines did not produce the corresponding products under the same reaction conditions (Scheme 1). This result indicated that the present protocol could be applicable to the chemoselective addition of aliphatic amines in the presence of aromatic amines.



Scheme 1 The chemoselectivity of the catalyst.

3.6 The TG and XRD analyses of the catalyst K_2CO_3/MgO

In order to investigate the active sites in the catalyst

K_2CO_3/MgO , the TG analysis (Figure 2) was made and the results showed that there was a slight weight loss at 500–550°C, indicating the decomposition of K_2CO_3 . In order to confirm the results, the base strength measured through Hammett-index gave the pK_a between 15 and 18.4, while K_2CO_3 was below 15. The stronger base site was obtained by decomposition of K_2CO_3 . Also, the interaction between K_2CO_3 and MgO was obvious. The decomposing temperature of K_2CO_3 in the catalyst K_2CO_3/MgO was reduced to 650°C. The stronger base site K_2O here must have an important effect on the reaction for the yield was improved much as to K_2CO_3 even if the catalyst amount was reduced. The XRD analysis of the catalyst was carried out. The result showed that the difference between the catalyst and the carrier MgO was obvious with the peaks disappearing when K_2CO_3 was supported on the carrier, which indicated the strong interaction between K_2CO_3 and MgO and the high dispersion of the active sites. The base amount of stronger sites and base sites determined by CO_2 -TPD showed that the stronger base sites were about 5% of the total base amount, which indicated that about 5% K_2CO_3 was decomposed during the thermal treatment.

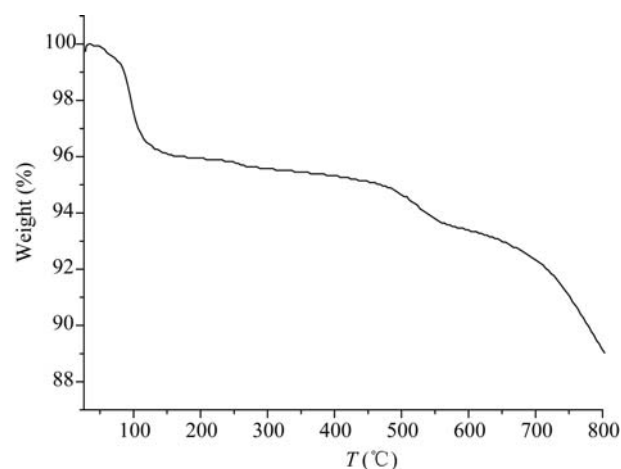


Figure 2 The TG of the catalyst K_2CO_3/MgO .

4 Conclusions

In conclusion, a novel efficient procedure has been developed for the conjugate addition of amines to electron deficient alkenes. Operational simplicity without any solvent, low cost of the catalyst used, high yields, excellent chemoselectivity, and wide applicability are the key features of this methodology.

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