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# Solid Superbase-Catalyzed Stereoselective 1,4-Addition Reactions of Simple Amides in Batch and Continuous-Flow Systems

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**Abstract.** The utilization of a catalytic solid superbase in fine synthesis is challenging. Here, we employed  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalytically as a highly efficient solid superbase to perform direct 1,4-addition reactions of simple amides with  $\alpha$ , $\beta$ -unsaturated carbonyls. The desired 1,5-dicarbonyl compounds were obtained in high yields with excellent *anti*-diastereoselectivities.  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> showed a Hammett basicity of  $37>H_{\geq}$  35. The solid base was characterized by using TGA-DTA, <sup>27</sup>Al solid-state NMR spectroscopy, and XPS to determine the origin of the superbasicity. Continuous-flow

Introduction

A solid base with a base strength of  $H \ge 26$  can be defined as a superbase.<sup>[1]</sup> Like other solid bases, a superbase possesses several advantages over liquid bases and organometallics, such as less production of waste chemicals, no requirement for neutralization of reaction mixture, easy separation and potential reuse of the base, and the bases can be used in hightemperature reactions.<sup>[2]</sup> In addition, the use of a solid superbase as a catalyst can be superior to other solid bases in terms of selectivity and their use can reduce the extent of tarring during the reaction.<sup>[3]</sup> However, superbases are extremely susceptible to various acidic entities such as moisture and CO<sub>2</sub>. As a consequence, reports on the exploration of superbase catalysts in fine chemistry are scarce. Despite these shortcomings, superbase catalysts have been shown to deliver excellent catalytic performance and stability in various reactions on academic and industrial scales.<sup>[4]</sup> Therefore, superbases have attracted attention as potential candidates for use in various reactions, particularly in the area of stereoselective and asymmetric catalysis.

Carbon–carbon (C–C) bond-forming reactions using carbanions derived from pronucleophiles with catalytic amounts of Brønsted bases under proton transfer conditions are one of the most efficient methods from the standpoint of atom economy.<sup>[5]</sup> However, this catalytic approach becomes challenging for pronucleophiles containing weakly acidic protons (p $K_a > 30$  in DMSO) because of lethargic deprotonation, and only strong Brønsted synthesis of a 1,5-dicarbonyl compound was demonstrated by using the novel solid superbase-catalyzed 1,4-addition methodology. We have also uncovered the potential of  $K/\gamma$ - $Al_2O_3$  in asymmetric 1,4-addition reactions.

**Keywords:** K/γ-Al<sub>2</sub>O<sub>3</sub>; Solid superbase; 1,4-addition reactions; Heterogeneous catalysis; Flow synthesi

bases (e.g., lithium diisopropylamide (LDA), alkyllithium) can afford the corresponding carbanions. The catalytic use of such strong Brønsted bases is extremely difficult because the acidity of the corresponding conjugate acids is intrinsically too low to regenerate bases through deprotonation by reaction intermediates. On the other hand, recently, we have developed Brønsted base-catalyzed C-C bondforming reactions of weakly acidic pronucleophiles under homogeneous conditions by making use of strongly basic reaction intermediates, termed product bases.<sup>[6]</sup> In this strategy, the reaction intermediates are designed to possess sufficiently strong basicity to deprotonate fewer acidic hydrogen atoms of the next pronucleophiles to achieve the catalytic turnover. Our group has already employed this strategy to achieve catalytic stereoselective addition reactions of simple esters,<sup>[6b,c]</sup> amides,<sup>[6a]</sup> alkylazaarenes,[6d] and others.<sup>[6e,f]</sup> In this context, it is worth noting that the 1.4-addition reactions of carbonvl compounds with  $\alpha,\beta$ -unsaturated carbonyl compounds are elegant yet challenging C–C bond-forming methods for constructing 1.5-dicarbonyl compounds. Several methodologies for 1.4-addition reactions were developed, primarily by introducing activating groups on nucleophilic partners.<sup>[7]</sup> Recently, our group demonstrated catalytic asymmetric 1,4-addition reactions of simple amides that do not bear any activation groups, by using a product base mechanism in the presence of catalytic amounts of KHMDS and a chiral macrocyclic crown ether as a homogeneous catalyst. The method afforded the desired 1,4-adducts in high yields with high stereoand enantioselectivities.<sup>[6a]</sup> It is, however, pertinent

methodologies that these are restricted to homogeneous catalysis in a batch system. Therefore, we recognized the necessity to develop a simple and selective heterogeneous catalytic system that would allow 1,4-addition reactions to be performed under flow conditions. both batch and Recently, continuous-flow synthesis has drawn much attention in the field of organic synthesis because of its several advantages over batch systems in terms of environmental compatibility, efficiency, and safety.<sup>[8]</sup> These advantages have inspired our group to develop several methodologies for continuous-flow synthesis with various heterogeneous catalysts.<sup>[9]</sup> Very recently we have demonstrated stereoselective 1,4-addition reactions catalyzed by a solid base under continuousflow synthesis.<sup>[9d]</sup> Thus, we envisaged that solid superbases can be utilized as heterogeneous catalysts to achieve stereoselective 1,4-addition reactions of simple amides under a batch system, which can be further tailored to a continuous-flow system.

#### **Results and Discussion**

We began our investigation of the stereoselective 1,4addition of N,N-diphenylpropionamide (1a) to the pyrrolidine derivative of cinnamide by using various solid superbases, as shown in Table 1 (see Table S1 in the Supporting Information for details of the screening). The initial trials indicated that potassium (K) dispersed on magnesium oxide (K/MgO) and gamma ( $\gamma$ )-alumina (K/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub>) promoted the desired 1,4-addition reaction catalytically (Table 1, entries 1 and 2). In contrast, metallic K and a physical mixture of K and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> did not catalyze the 1,4-addition (entries 3 and 4), indicating the presence of a synergistic effect of both entities in the case of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub>. CsF/Al<sub>2</sub>O<sub>3</sub>, reported by us recently, did not promote this reaction at all (entry 5).<sup>[9d]</sup> The high yield and improved stereoselectivity encouraged us to employ  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> for further investigations.

**Table 1.** Optimization of reaction conditions for thecatalytic 1,4-addition reaction using solid superbases.

ο

Ph O

0

0 U	Ph	Solid supe	erbase (10 mg)			
Ph <sub>2</sub> N 1a, 0.3 r	nmol <b>2a</b> , 0.2 m	3aa, 1,4-adduct				
En try	Solid superbase	<b>3a</b> , 1,4-ad	duct	Comment		
		Yield (%) <sup>a</sup>	anti/syn a	-		
1	K/MgO	51	84:16	20 wt% of K on MgO		
2	K/γ-Al <sub>2</sub> O <sub>3</sub>	55	90:10	20 wt% of K on $\gamma$ -Al <sub>2</sub> O <sub>3</sub>		
3	Κ	15	80:20	K amount is		
4	$\begin{array}{c} K + \gamma \text{-} \\ Al_2O_3 \end{array}$	no reaction	_	20 wt% of K mixed with γ-		
				$A_{12}$		

5 <sup>b</sup>	CsF/Al <sub>2</sub> O <sub>3</sub>	no		40 wt% of		
		reaction	. (	CsF on	$Al_2O_3$	
1 Dot	armined by <sup>1</sup> H	I NMP a	nalveie (crude)	<sup>b</sup> The	reaction	

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis (crude). <sup>b</sup> The reaction was performed at rt.

Several  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> samples were prepared by following the procedure depicted experimental section, in which  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> was subjected to thermal pre-treatment under vacuum at various temperatures. The activity of these superbasic solid bases toward the 1,4-addition reaction was evaluated. The obtained results (Table S2) revealed the profound effect of the thermal treatment on the activity of the  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub>; 600 °C was considered to be optimal for this purpose (Table S2, entry 4). When the activity of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> was evaluated as a function of K loading on  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>, a loading of 20 wt% gave the best catalytic performance (Table S3). With the best solid superbase in hand, we screened electrophiles and found that the use of N,N-dimethylcinnamide (2c) as a limiting substrate could improve the yield and diastereoselectivity of the desired 1,4-adduct significantly (Table S4). After the screening of other reaction parameters namely solvents, concentration and catalyst amount (Table S5 and Table S6), the 1,4addition reaction proceeded even with 4 mg of  $K/\gamma$ - $Al_2O_3$  (i.e., 10 mol% with respect to K) to afford the quantitatively 97:3 1,4-adduct with anti-



diastereoselectivity (Table S6, entry 4).

**Figure 1.** a) TGA\_DTA curve of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>; <sup>27</sup>Al solid-state NMR spectra of b)  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> thermally treated at 600 °C and c) K/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub>; XPS spectra of K/ $\gamma$ -Al<sub>2</sub>O<sub>3</sub>: d) K 2p region, e) O 1s region, and f) Al 2p region.

We estimated the Hammett basicity of the best  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> based on titration experiments using Hammett indicators (Figure S1).  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> showed a super basicity of  $37>H_{\geq}35$  and the amount of superbasic site responsible for 1,4-addition reactions was quantified as 1.36 mmol/g (Table SA). In other words, 4 mg of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> under optimal catalytic conditions presents 2.7 mol% of actual superbasic sites (Table SB).

The TGA-DTA curve of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> indicated a weight loss up to 240 °C due to desorption of physiand chemisorbed water, CO<sub>2</sub>, and volatile organic molecules (Figure 1a). Further weight loss after 400 °C was produced by dehydroxylation.<sup>[10]</sup> However, the thermal treatment above 600 °C also facilitates the phase transformation of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> into  $\theta$ -Al<sub>2</sub>O<sub>3</sub>.<sup>[10a]</sup> On the other hand, the <sup>27</sup>Al solid-state NMR spectra of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> thermally treated at 600 °C showed two peaks corresponding to two different local electron densities at the aluminum (Al) nucleus produced by the neighboring oxygen (O) atoms (Figure 1b). The peak at 15 ppm is typical of Al in O-octahedra, and the peak located at 74 ppm is assigned to Al in Otetrahedra.<sup>[11]</sup> After comparing the <sup>27</sup>Al solid-state NMR spectra of  $\gamma$ -alumina before and after thermal treatment, it was evident that the ratio of the number of Al in O-tetrahedra to the same in O-octahedra increased because of both desorption of water and dehydroxylation processes. The oxygen deficiency in the crystalline structures of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> due to the thermal treatment creates octahedral vacant sites on the surface. Therefore, the thermal treatment of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> at 600 °C removes adsorbed water, destroys the hydrogen bonding, and dehydroxylates the surface, creating cationic defect sites primarily generated from octahedral sites.<sup>[10a]</sup> Upon dispersion of the melted K on the thermally treated  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>, K ionized to form a cation (K<sup>+</sup>) and the released electron is trapped in oxygen-deficient cationic defect sites of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>. The trapped electron localized to nearby  $O_2^-$ , increasing the electron density of  $O_2^-$  to create superbasic sites similar to the phenomenon observed in the case of K/MgO.<sup>[12]</sup> On the other hand, K remained captured in the octahedral vacant sites on the dehydroxylated surface of  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>, leading to a type of strong host-guest interaction in the same fashion as in KNO<sub>3</sub>/y-Al<sub>2</sub>O<sub>3</sub>.<sup>[4,13]</sup> Consequently, the Al nucleus surrounded by superbasic O experienced high electron density, larger than that produced by a typical O-tetrahedra and similar to that produced by the O-octahedra. Therefore, the <sup>27</sup>Al solid-state NMR spectrum of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> showed enhancement of the signal centered at 15 ppm (Figure 1c). We also performed XPS analysis of K/y-Al<sub>2</sub>O<sub>3</sub>, which provided supporting evidence for two types of O species, with peaks centered at 530 eV and 529 eV (Figure 1e). The O with lower binding energy can be attributed to the superbasic site with high electron density. In contrast, the deconvoluted high-resolution XPS spectrum of the O 1s region did not show similar superbasic O with lower binding energy when  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> was prepared from the  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> without any thermal treatment (Figure S5e). In the case of Al, two peaks centered at 73.2 eV and 72.7 eV can also be correlated to the Al surrounded by O-octahedral and O-tetrahedral, respectively (Figure 1f).

With the optimal conditions in hand, the substrate scope for the  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyzed stereoselective 1,4addition reactions were examined (Table 2). Excellent yield and *anti*-diastereoselectivity of the 1.4-addition reaction were achieved for the cinnamide (3ac). High yields were maintained by changing the position of the methyl substituent on the aromatic ring of the cinnamamide (3ad-f). However, the antidiastereoselectivities decreased marginally in the order p > m > o-substitution.  $\alpha,\beta$ -Unsaturated amides bearing either electron-rich or electron-deficient substituents on the aromatic moiety gave the desired products in high yields with high antidiastereoselectivities (**3ag**-j). Outstanding diastereoselectivity with high yield was accomplished for the 2-furyl substituted  $\alpha,\beta$ -unsaturated amide when the amount of catalyst was increased slightly (3ak). The steric bulk of the hindered aromatic ring affected neither the yield nor the stereoselectivity of the desired 1,4-adduct (3al). Furthermore, the 1,4addition reactions with linear  $\alpha,\beta$ -unsaturated amides also proceeded to afford the corresponding antidiastereomers with good to excellent yields (3am, **3an**). Other aliphatic  $\alpha,\beta$ -unsaturated amides containing branched and cyclic moieties also underwent the desired 1,4-addition under modified conditions (**3ao**, **3ap**). The use of butyramide (**1b**) as nucleophile also worked smoothly and proceeded. with high yield and with excellent diastereoselectivity.

**Table 2.** Substrate scope of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyzed 1,4-addition reactions of simple amides.<sup>a</sup>

	<sup>1</sup> + R <sup>2</sup>	ν N toluene	Al <sub>2</sub> O <sub>3</sub>	→ Ph <sub>2</sub> N	
<b>1</b> , 1 equiv	<b>2</b> , <sup>-</sup>	24 h, 1.5 equiv	-40 °C		R <sup>1</sup> 3, 1,4-adduct
Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	3	Yield	anti/syn
				(%)	
1	-CH <sub>3</sub>	Ph	3ac	97	97:3
2	-CH <sub>3</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	3ad	98	98:2
3	-CH <sub>3</sub>	<i>m</i> -MeC <sub>6</sub> H <sub>4</sub>	3ae	88	94:6
4	-CH <sub>3</sub>	o-MeC <sub>6</sub> H <sub>4</sub>	3af	93	92:8
5 <sup>b</sup>	-CH <sub>3</sub>	<i>p</i> -	3ag	97	97:3
		MeOC <sub>6</sub> H <sub>4</sub>			
6	-CH <sub>3</sub>	p-FC <sub>6</sub> H <sub>4</sub>	3ah	98	98:2
7°	-CH <sub>3</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	3ai	95	98:2
8°	-CH <sub>3</sub>	p-BrC <sub>6</sub> H <sub>4</sub>	3aj	95	98:2
9 <sup>d</sup>	-CH <sub>3</sub>	2-furyl	3ak	96	98:2
10	-CH <sub>3</sub>	1-naphthyl	3al	92	97:3
11	-CH <sub>3</sub>	Me	3a	91	98:2
			m		
12 <sup>e,f,g</sup>	-CH <sub>3</sub>	pentyl	3an	98	95:5
$13^{d,e,g,h}$	-CH <sub>3</sub>	<sup>i</sup> Pr	3ao	81	81:19
$14^{b,d,f,g}$	-CH <sub>3</sub>	Су	Зар	90	97:3
15 <sup>e</sup>	-	Ph	3bc	98	>99/<1
	$C_2H_5$				

<sup>a</sup> The reaction of **1a** (0.2 mmol) with **2** (0.3 mmol) was carried out in toluene (0.07 M) at -40 °C for 24 h using

K/γ-Al<sub>2</sub>O<sub>3</sub> (4 mg) unless otherwise noted. <sup>b</sup> K/γ-Al<sub>2</sub>O<sub>3</sub> (6 mg). <sup>c</sup> Reaction time 36 h. <sup>d</sup> Reaction time 48 h. <sup>e</sup> K/γ-Al<sub>2</sub>O<sub>3</sub> (8 mg). <sup>f</sup> -20 °C. <sup>g</sup> **2** (0.4 mmol). <sup>h</sup> -10 °C.

Hot filtration tests revealed no detectable catalysis in the solution phase, indicating that no metal leaching occurred (see the experimental section in the Supporting Information). This result implied that the enolate (a in Scheme 1) stabilized on the surface of the solid superbase after deprotonation of the amide, which reacted with the electrophile to form a surfacebound anionic "product base" (b in Scheme 1). According to our proposed mechanism (Scheme 1), the "product base" can either be protonated by the conjugate acid of the base to afford the desired product with regeneration of the superbase catalyst (PATH A) or deprotonate the next pronucleophile to achieve catalytic turnover (PATH B). When a mixture of N.N-diphenvlpropionamide (1a) and N.Ndimethylpropionamide (1b) was employed in the same 1,4-addition reaction, the 1,4-adduct was quantitatively afforded exclusively from the former (1a) (Table S8). It is known that  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> does not have sufficient basicity to deprotonate 1b (Table S7), whereas the "product base" (b in Scheme 1) is capable of deprotonating the same through PATH B. Given that no trace of **3bc** was observed, we believe that PATH A is preferred over PATH B, leading to catalyst regeneration upon complete consumption of 1a, probably because of the higher acidity of the conjugate relative to the nucleophile.



**Scheme 1.** Plausible reaction mechanism for  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyzed 1,4-addition reaction of simple amide.

Although our solid base catalyst demonstrated the robustness against the leaching confirmed by the filtration experiments, we failed to demonstrate the catalyst recovery and reuse in the batch system. Being superbasic in nature,  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> is extremely susceptible to the ambient atmosphere and as a result, the basicity was diminished irreversibly during the process of recovery by the simple filtration, and washing. Since our solid catalyst demonstrated a firm intrinsic heterogeneity, we envisaged that a successful execution of *Type IV* flow synthesis<sup>[8d]</sup> could supersede the disadvantage of the catalysis in the batch system and the exploitation of the benefit of

the solid base will be justified up to the fullest. With that motivation, we attempted to develop a continuous-flow synthesis of **1ac** based on our novel methodology (Scheme 2). For this purpose, a glass column (10 mm diameter and 50 mm length) was packed with 400 mg of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> (Scheme S2). The catalyst was diluted by an equal amount of Celite and approximately 2.0 g of sea sand. Such dilution improved the productivity by increasing the residence time of the substrates. The bigger diameter of the reactor column and the use of sea sand as diluent markedly reduced the back pressure generated by the catalytic bed inside the reactor column and hence helped to achieve a stable continuous flow throughout the flow synthesis. Keeping 0.05 M as a fixed concentration of **1a**, a flow rate of 0.06 mL/min was accepted as the optimal rate (see Figure S10). The results indicated that the flow system could be used to effectively produce the desired 1,4-adduct on the solid catalyst with excellent diastereoselectivity that was comparable with that of the batch system. With the optimized reaction conditions in hand, the desired 1,4-adduct (3ac) was continuously synthesized for a period of 48 h with high yield (86%) and notably high anti/syn selectivity for the 1,4-adduct (97:3, see Figure S11). The TON for the flow synthesis was calculated to be 14 (Figure S11) whereas the same for a batch system of 0.2 mmol scale with comparable substrate/catalyst to the flow (Table S4, entry 5 in the SI) was 11.5.



**Scheme 2.** Schematic diagram of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyzed 1,4 addition reaction in continuous-flow reactor.

A preliminary trial of an asymmetric variant of the  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyzed 1,4-addition reaction was performed in the presence of a catalytic amount of a chiral macrocyclic crown ether.<sup>[6a]</sup> After the optimization of the ratio of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub>/ligand (Table S9) the 1,4-addition reaction of simple amide **1a** with **2c** proceeded in high yield (95%) with excellent enantioselectivity (95%) and high diastereoselectivity (>99/<1) (Scheme 2). To our knowledge, this is the first example of the catalytic utilization of solid superbase in an asymmetric addition reaction, although the nature of the active species remains unknown.



Scheme 3.  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub> catalyzed asymmetric 1,4-addition reaction of amide.

### Conclusion

In summary, we have developed an efficient methodology for the stereoselective 1,4-addition reactions of simple amides that do not bear any activating group, catalyzed by K/y-Al<sub>2</sub>O<sub>3</sub> as a solid superbase. Several  $\beta$ -substituted  $\alpha$ , $\beta$ -unsaturated amides as electrophiles gave the desired 1,4-adducts in high yields with excellent diastereoselectivities. We identified the origin and quantified the amount of the superbasic species on the surface of  $K/\gamma$ -Al<sub>2</sub>O<sub>3</sub>. We also demonstrated the continuous-flow synthesis of a 1,5-dicarbonyl compound by using the K/γ-Al<sub>2</sub>O<sub>3</sub> catalyst, and demonstrated for the first time the feasibility of the asymmetric 1,4-addition reaction catalyzed by solid superbase in the presence of a chiral crown ether. Further investigations focused on applying this solid base to other reactions are in progress.

## **Experimental Section**

**Typical preparation of K/\gamma-Al<sub>2</sub>O<sub>3</sub>: A typical procedure represents the synthesis of K/\gamma-Al<sub>2</sub>O<sub>3</sub> with 20 wt% loading of K on \gamma-Al<sub>2</sub>O<sub>3</sub>. 0.80 g of \gamma-Al<sub>2</sub>O<sub>3</sub> was thermally treated at 600 °C under vacuum for 3 h. After that, \gamma-Al<sub>2</sub>O<sub>3</sub> was brought back to the room temperature and mixed with 0.2 g of K inside the glove box in a 30 mL flask and it was closed by a two-way stopper. The mixture was kept strictly under Ar atmosphere outside the glove box using a balloon filled with Ar through the two-way stopper. After that the solid mixture was stirred with increasing temperature in a heating bath under vacuum using a pump. K started to melt after 65 °C and the temperature was allowed to rise up to 110 °C. The black colored solid mixture was allowed to stir at 110 °C for 10 min and then let the mixture to cool down to room temperature. Once the resultant black colored K/\gamma-Al<sub>2</sub>O<sub>3</sub> reached room temperature, it was stored inside the glove box at -20 °C.** 

Typical experimental procedure for K/γ-Al<sub>2</sub>O<sub>3</sub> catalyzed 1,4-addition reactions of simple amides (1) with *α*,β-unsaturated carbonyl compounds (2): A typical procedure represents the reaction of propionamide (1a) with *N*,*N*-dimethylcinnamide (2c). In a glovebox, K/γ-Al<sub>2</sub>O<sub>3</sub> (4 mg, 5.44 µmol of superbasic site) and propionamide (45 mg, 0.20 mmol) (1a) were added to a 10 mL flame-dried flask. The flask was cooled down to -40 °C. At this temperature 2 mL of dried toluene (2.0 mL) was added and the resulting mixture was stirred for 30 min at -40 °C (Flask A). In the meantime, 2c (52.6 mg, 0.300 mmol) was placed in a flame-dried flask inside the glove box and was dissolved in 1.0 mL of dried toluene (Flask B). Flask B was also cooled down to -40 °C and was slowly added to Flask A after 30 min of stirring through a cannula. The resultant reaction mixture was stirred at -40 °C for 24 h. The reaction was quenched simply by separating the catalysts through simple filtration. After filtration, the solvent was evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (hexane:ethyl acetate = 2:3) to afford  $N^5$ , N<sup>5</sup>, 2-trimethyl-N<sup>1</sup>, N<sup>1</sup>, 3-triphenylpentanediamide (3ac) (78.9 mg, 98%).

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