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Catalytic Stereoselective 1,4-Addition Reactions Using CsF on Alumina as Solid Base: A Heterogeneous Platform for Continuous-Flow Synthesis of Glutamic Acid Derivatives

Parijat Borah, Yasuhiro Yamashita, and Shū Kobayashi*[a]

Abstract: A novel methodology using $CsF{\cdot}Al_2O_3$ as a highly efficient, environmentally benign and reusable solid base catalyst was developed to synthesize glutamic acid derivatives via stereoselective 1,4-addition of glycine derivatives to α,β-unsaturated esters. $CsF{\cdot}Al_2O_3$ showed not only great selectivity toward 1,4-addtion reactions by suppressing undesired formation of pyrrolidine derivations via [3+2] cycloaddition, but also offered high yields for the 1,4-adduct with excellent *anti* diastereoselectivities. The catalyst was well characterized by using XRD, ^{19}F MAS-NMR, ^{19}F NMR, FT-IR, CO_2-TPD, and XPS, and highly basic F from the Cs_3AlF_6 was identified as the most probable active basic site for the 1,4-addition reactions. Continuous-flow synthesis of 3-methyl glutamic acid derivative was successfully demonstrated by using the solid base-catalyzed methodology.

The generation of carbanion by using a base is one of the key steps in numerous organic reactions, and extensive studies have been made to investigate various base-catalyzed organic reactions.[1] Compared with liquid bases or organometallics, solid base catalysts possess many advantages such as less production of waste chemicals, no requirement of neutralization of reaction mixture, easy separation of the catalysts from products as well as possibility of catalyst reusability, scope for high temperature reactions, etc.[2] However, the exploration of solid base-catalyzed organic reactions is still in an inadequate level even after half century since the first report of solid base in spite of various challenges associated with the replacement of liquid bases for solids.[3] Alkali metal fluorides such as KF or CsF on alumina are potential solid bases and have been explored extensively in wide range of organic reactions except only a few examples of stereoselective solid base catalysts. Surprisingly, their basic strength as well as identification of their active phases are still under debate.[4] Furthermore, ambiguity about heterogeneity of the basic sites of these solid bases still prevails according to certain reports.[5] Therefore, it is crucial to identify actual catalytic basic sites for the development of an efficient methodology in particular stereoselective synthesis using these solid bases as reusable heterogeneous catalysts.

On the other hand, β-substituted derivatives of glutamic acid are essential nutrients for mammals, including humans, for their vital role as structural components of peptides and proteins, as well as a key ingredient in numerous biochemical pathways.[6] Catalytic stereoselective 1,4-addition of glycine derivatives to α,β-unsaturated carbonyl compounds or other Michael acceptors is one of the effective synthetic routes for the synthesis of glutamic acid and its β-substituted derivatives.[7] However, such synthetic methodologies are still not adequate due to low stereoselectivity at the β-position, especially in β-alkyl substituted products. In addition, undesired [3+2] cycloaddition undergoes easily when Lewis acids are employed for the stereocontrol.[8] Soloshonok et al. reported highly stereoselective 1,4-additions for the synthesis of β-alkyl substituted derivatives of glutamic acid, although these methodology required specially designed chiral/achiral Ni(II) complexes of glycine Schiff bases as substrates to achieve high selectivity.[9] While several catalytic disastereoselective methodologies have been developed for this purpose,[10] in most of these methods, cyclic α,β-unsaturated carbonyl compounds[10b, 10d, 11] or β-aryl[12] and β-CF_3,[10e, 13] β-ROCO [10a, 10f, 14] substituted acyclic α,β-unsaturated carbonyl compounds were employed, and highly diastereoselective 1,4-additions of conventional simple Schiff bases of glycine esters to β-alkyl substituted α,β-unsaturated carbonyl compounds were scarcely reported. Recently our laboratory has reported such 1,4-addition reactions of glycine derivatives with acyclic β-alkyl α,β-unsaturated carbonyl compounds using chiral alkaline earth metal complexes as catalysts in the presence of a catalytic amount of Brønsted base.[8, 15] In these reports, however, we were often suffered from [3+2] cycloaddition as side reactions to afford substituted pyrrolidine derivatives, and the selectivity for 1,4-addition reactions over the cycloaddition has been achieved by the use of more sterically hindered protecting groups of the amine parts as well as by employing Lewis acidic alkaline earth metal complexes in homogeneous catalytic systems. For the supply of β-substituted glutamic acid derivatives, more simple and selective systems under heterogeneous conditions are highly demanded. Herein, we report for the first time an efficient and environmentally benign methodology to synthesize the β-substituted glutamic acid derivatives, via 1,4-addition of a simple glycine Schiff base to β-substituted α,β-unsaturated esters, using a solid base as a heterogeneous base catalyst under mild conditions.

We began our investigation of stereoselective 1,4-addition of a glycine Schiff base (**1a**) to methyl crotonate (**2a**) in combination with various solid bases as shown in Table S1 in the supporting information (SI). The initial trials indicated that $CsF{\bullet}Al_2O_3$ (pre-treated at 200 ˚C) promoted the desired catalytic 1,4-addition reaction with high diastereoselectivity for the *anti*-1,4-adduct. Further optimization of the reaction conditions using $CsF{\cdot}Al_2O_3$ is summarized in Table 1 (complete table in Table S3 in the SI). The solvent screening showed that relatively polar solvents were effective for the reaction, and that THF was found to be the best solvent. Low catalyst loading and high concentration were found to be favourable for 1,4-addition as well as *anti*-diastereoselectivity. Under the optimal conditions, $CsF{\cdot}Al_2O_3$ offered the highest yield of 98% for the desired **3aa** at

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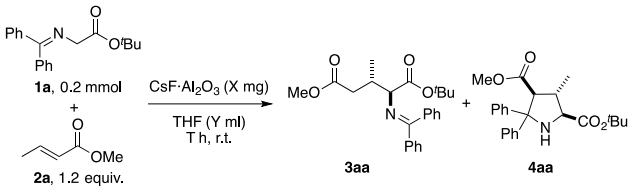
a catalyst loading of 2 mol% (*w.r.t* CsF) within a short reaction time (1 h) (Table 1, entry 4).

Table 1. Optimization of reaction conditions for catalytic 1,4-addition reaction using $CsF{\cdot}Al_2O_3$ as solid base.



Entry	X mg	Mol% CsF.Al_2O_3	of Time (h)	Y ml (M)	Conversion of **1a** (%)	**3aa**:**4aa**	**3aa**[a] Yield (%)	*anti:syn*
1	30	39.5	0.5	4 (0.05)	100	96:4	96	96:4
2	5	6.6	0.5	1 (0.2)	100	98:2	96	98:2
3	2	2.6	0.5	1 (0.2)	100	98:2	97	>99:1
4	**1.5**	**2.0**	**1**	**1 (0.2)**	**100**	**98:2**	**98**	**>99:1**
5	1	1.3	1	1 (0.2)	96.3	98:2	96	>99:1

[a] Determined by ^{1}H NMR analysis (crude).

Several $CsF{\cdot}Al_2O_3$ samples were prepared followed by the thermal treatment under vacuum at various temperatures such as 120, 170, 200, 300, 400 and 500˚C. $CsF{\cdot}Al_2O_3$ without any thermal treatment showed negligible catalytic activity (Table S5, entry 1 in the SI) in spite of possessing basic sites originated from the F^- of impregnated CsF (Fig S10 in the SI). This catalyst contains surface adsorbed water and CO_2 which poisoned the basic sites.[5] Thus, increase in the catalytic activity was observed as the thermal treatment increases from 120 ˚C to 200 ˚C (Table S5, entries 2-4) and thermally treated at 200 ˚C was found to be optimal for the catalytic 1,4-addition with strong basicity as indicated by CO_2-TPD (Fig S10). The XRD patterns of these catalysts showed the appearance of a strong signal centred at 2θ = 27.3˚ corresponding to Cs_3AlF_6 (Figure 1).[16] ^{19}F MAS NMR studies also revealed that the chemical shift at -95 ppm attributed to F^- from CsF disappeared in the optimal catalyst and a new signal appeared at -114 ppm attributed to AlF_6^{3-}(Fig. S1 and S2).[16] An additional ^{19}F NMR analysis also advocated the absence of free CsF in this catalyst (Fig S14) and the FTIR transmittance analysis confimed the formation of Cs_3AlF_6 (Fig S13). Similar high catalytic activities were also observed for the catalysts treated at 300 and 400˚C with a minuscule declination in the selectivity. XRD patterns of these two catalysts also showed the presence of crystalline phase of Cs_3AlF_6 along with other phases such as β-$CsAlF_4$ and $CsAl_2F_7$. A complete loss of basicity (Fig S10) and thereby catalytic activity (Table S5) was observed for $CsF{\bullet}Al_2O_3$ treated at 500˚C due to the presence of less crystalline Cs_3AlF_6 phase resulted by sintering. The FTIR transmittance analysis confimed signals ascribed to $CsAlF_4$ and AlF_3 for the samples pretreated at 300˚C and 500˚C (Fig S13). Furthermore, XRD studies also indicated a gradually decrease of the crystalline size of Cs_3AlF_6 phase when the loading of CsF was less than 40 wt% (Fig S12) resulting a significant downfall in the reactivity (Table S4). The XPS analysis indicated that less than 40 wt% loading of CsF cannot afford complete surface coverage by the Cs_3AlF_6 (XPS analysis in the SI). On the other hand, catalyst with 60 wt% loading of CsF on alumina contains CsF phase alongside the crystalline Cs_3AlF_6 phase as indicated by XRD (Fig S12) and the additional ^{19}F NMR analysis (Fig S14). This dispersed F^- on alumina from the impregnated CsF can catalyse the reaction in homogeneous fashion [5] resulting low selectivity (Table S4, entry 1). On the other hand, the basicity of the best catalyst is an outcome of the interaction of Cs^+ of the crystalline phase of Cs_3AlF_6 with the O atom from the support which not only generates basicity on the O species but also lead the negative charge to be localized more on F atom resulting strong basic F containing sites (detail discussion in the XPS section in the SI).

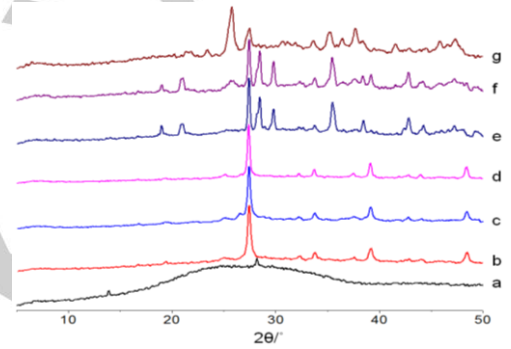
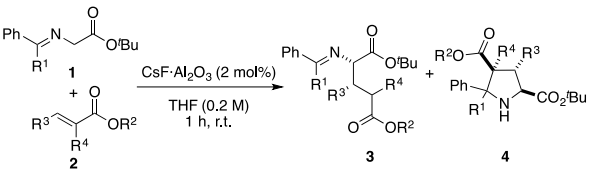


Figure 1: XRD patterns of various samples of $CsF{\cdot}Al_2O_3$: (a) without thermal treatment and thermal treatment at (b) 120 ˚C, (c) 170 ˚C, (d) 200 ˚C, (e) 300 ˚C, (f) 400 ˚C, (g) 500 ˚C. Indexed XRD patterns are available in the Fig S11.

Table 2. Substrate scope for catalytic 1,4-addition reaction using $CsF{\cdot}Al_2O_3$ as solid base.



Entry	R^1	R^2	R^3	R^4	1,4-adduct	1,4:[3+2][a]	1,4 adduct Yield (%)	1,4 adduct *anti:syn*[a]
1	Ph	Me	Me	H	**3aa**	98:2	96	>99:1
2	^{i}Pr	Me	Me	H	**3ba**	-	0	-
3	^{t}Bu	Me	Me	H	**3ca**	-	0	-
4	Ph	^{i}Pr	Me	H	**3ab**	97:3	94[c]	>99:1
5	Ph	^{s}Bu	Me	H	**3ac**	98:2	96[d]	>99:1
6	Ph	Bu	Me	H	**3ad**	98:2	95[d]	>99:1
7	Ph	Me	H	H	**3ae**	99:1	quant	-
8	Ph	Me	H	Me	**3af**	-	82	50:50[b]

9	Ph	Me	Et	H	**3ag**	98:2	86	98:2
10[e]	Ph	Me	Pentyl	H	**3aj**	95:5	86	92:8
11[g]	Ph	Me	Octyl	H	**3ah**	95:5	86	93:7
12[e]	Ph	Me	^{i}Bu	H	**3ai**	90:10	93	88:12
13[g,j]	Ph	Me	^{i}Bu	H	**3ai**	95:5	88	95:5
14[e]	Ph	Me	$Ph(CH_2)_2$-	H	**3ak**	82:18	88	88:12
15[g,j]	Ph	Me	$Ph(CH_2)_2$-	H	**3ak**	93:7	83	95:5
16[f]	Ph	Me	MeOCO-	H	**3al**	98:2	94	99:1
17[h]	Ph	Me	Ph-	H	**3am**	95:5	91	95:5
18[g]	Ph	Me	*p*-$NO_2C_6H_4$-	H	**3an**	91:9	88	88:12
19[g,j]	Ph	Me	*p*-$CF_3C_6H_4$-	H	**3ao**	98:2	92	97:3
20[g,j]	Ph	Me	*p*-FC_6H_4-	H	**3ap**	97:3	94	97:3
21[g,j]	Ph	Me	*p*-ClC_6H_4-	H	**3aq**	97:3	92	96:4
22[h,j]	Ph	Me	*p*-BrC_6H_4-	H	**3ar**	97:3	91	95:5
23[h,k]	Ph	Me	2-naphthyl	H	**3as**	97:3	92	98:2

[a] ^{1}H NMR analysis (crude). [b] 2,4-*Syn:anti*. [c] Reaction time: 8 h. [d] Reaction time: 5 h. [e] Reaction time: 12 h. [f] Reaction time: 3 h. [g] Reaction time: 24 h. [h] Reaction time: 48 h. [i] Solvent: diethyl ether (0.2 M). [j] Solvent: toluene:diethyl ether = 1:1 (0.2 M). [k] Solvent: toluene:diethyl ether = 2:1 (0.07 M).

With the optimal conditions in hand, the substrate scope for the CsF•Al_2O_3-catalyzed stereoselective 1,4-addition of various glycine Schiff bases with α,β-unsaturated esters were examined (Table 2). The investigations showed no reactivity when alkane substituted imine part of the glycine Schiff bases were used due to the presence of less acidic α-proton as compared to **1a** (entries 2 and 3). Similarly, low reactivity was observed when the steric bulk of the ester part of crotonate was increased (entry 4-6). For further expansion of this methodology, we investigated a range of α,β-unsaturated methyl esters. The reactions of **1a** with both methyl acrylate (**2e**) and methyl methacrylate (**2f**) proceeded in high yields although methyl methacrylate gave 1:1 of *syn/anti*-2,4 diastereomeric ratio. Further investigations revealed that the steric bulkiness of the β-substitution of α,β-unsaturated methyl esters had a negative influence on the reactivity as well as the selectivity. Substrates with a linear alkyl chain at the β-position of α,β-unsaturated methyl esters provided reasonable selectivity for the desired 1,4-adduct with higher diastereoselectivity (entries 9-11) as compared to those with a branched/substituted alkyl chain (entries 12 & 14). However, an improved selectivity was achieved by employing diethyl ether as solvent for these substrates in an expense of longer reaction time (entries 13 & 15). On the other hand, dimethyl fumarate offered good reactivity to form the desired product with good yield and selectivity (entry 16). We also investigated series of β-aryl-α,β-unsaturated methyl esters to form the corresponding *anti* 1,4-adducts. For these substrates role of solvent is inevitable. Methyl cinnamate (entry 17) and methyl 4-nitrocinnamate (entry 18) provided comparable reactivity in THF as solvent, although the former offered better selectivity. These results also indicated that electron withdrawing group-substituted aryl can enhance the reactivity markedly. A similar trend was also observed in the case of other electron withdrawing group-substituted β-aryl-α,β-unsaturated methyl esters (entries 19-22). Moreover, these substrates did not show any reactivity in THF as solvent. On the other hand, the addition of toluene enhanced the reactivity significantly and a combination of toluene and diethyl ether was found to be optimal for these substrates. 2-Naphthyl substituted α,β-unsaturated methyl esters also underwent 1,4-addition catalytically to offer the desired 1,4-adduct in high yield with high selectivity (entry 23).

CsF•Al_2O_3 as a heterogeneous solid base catalyst presented a tremendous reusability towards the 1,4-addition reaction with a consistent yield and selectivity up to four catalytic cycles (Table S6 in the SI). The hot filtration test was also carried out, and no detectable catalysis in the solution phase was observed indicating the absence of metal leaching (experimental section in the SI). The structural integrity and the regeneration of the basic sites of the recovered catalyst were confirmed by powder XRD, ^{19}F MAS-NMR and CO_2-TPD (Fig. S5, S6 and S15 in the SI). Furthermore, except CsF•Al_2O_3, few other solid bases containing cesium, basic-alumina as well as α-alumina and few liquid bases failed to act as base catalyst for this reaction (Table S7). As shown in the photograph in the SI, the colour of the white CsF•Al_2O_3 turned into yellow in the presence of Schiff base (Fig. S7) whereas the solution remained colourless. It implied that the enolate stabilized on the surface of the solid base after the deprotonation of glycine Schiff base as shown in the plausible mechanism. The catalysis on the surface effectively suppressed further [3+2] cycloaddition due to the steric hindrance. On the contrary, the entire reaction mixture turned yellow in the case of KF•Al_2O_3 indicating the enolates were in the solution due to the homogeneous nature of the active base species i.e. KF or liquid like F^-anion (see the discussion of Figs. S8 and S9 in the SI). Such homogeneous nature of the active base spices also cast a negative impact on the selectivity towards 1,4-adduct. Furthermore, the catalytic turnover and the reusability of KF•Al_2O_3 were not achieved.

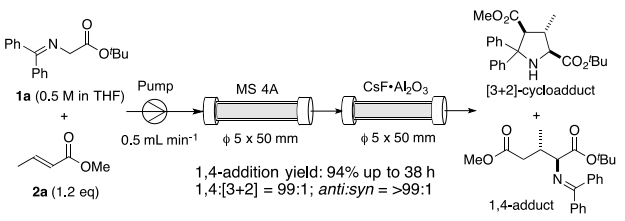


Figure 2. The schematic diagram of the continuous-flow reactor

Recently, continuous-flow synthesis draws much attention in the field of organic synthesis because of its several advantages over batch systems in terms of environmental friendliness, efficiency, and safety.[16] These advantages have inspired our group to develop several methodologies on continuous-flow synthesis with various heterogeneous catalysts.[17] Therefore, next, we attempted to develop a continuous-flow synthesis of the

derivative of 3-methylglutamic acid using our novel methodology (Figure 2). Keeping 0.5 M as fixed concentration of **1a**, a flow rate of 0.5 mL/min was accepted as the optimal rate (Table S9 in the SI). The results indicated that the flow system could effectively suppress the unwanted [3+2] cycloaddition primarily due to the short residence time of the desired 1,4-adduct on the solid catalyst. With the optimized conditions in hand, the desired 3-methylglutamic acid derivative was continuously synthesized for a period of 38 h with high yield (94%) and significantly high selectivity (1,4 addition/ [3+2] cycloaddition = 99:1; *anti*:*syn* for 1,4 adduct = >99:1) (Table S10 in the SI).

In summary, we have developed an efficient methodology for the synthesis of 3-substituted glutamic acid derivatives via stereoselective 1,4-addition of glycine derivatives to α,β-unsaturated esters in the presence of $CsF{\cdot}Al_2O_3$ as a robust recyclable solid base catalyst. Several β-substituted α,β-unsaturated esters, notably, β-alkyl substituted α,β-unsaturated esters gave the desired adducts in high diastereoselectivities. It was found that $CsF{\cdot}Al_2O_3$ could suppress the unwanted formation of pyrrolidines derivations via [3+2] cycloaddition, which was otherwise predominant over the 1,4-addtion reaction. We recognized an interaction of Cs^+ from the crystalline phase of Cs_3AlF_6 with the O atom form the support is responsible for the generation of active site in the best catalyst. We also successfully demonstrated the continuous-flow synthesis of the 3-methyl glutamic acid derivative by using the $CsF{\cdot}Al_2O_3$ catalyst. Further investigation to apply this solid base to other reactions is in progress.

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Keywords: alkali metal fluorides on alumina • β-Glutamic acid derivatives • flow synthesis • solid base • stereoselective addition reactions

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Layout 1:

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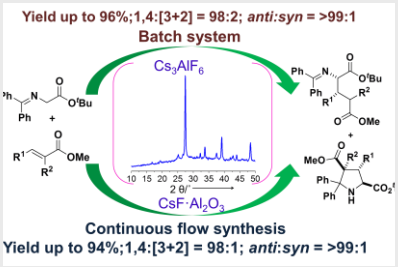
Made our base solid: A novel methodology to synthesize glutamic acid derivatives via highly stereoselective 1,4-addition of glycine derivatives to α,β-unsaturated esters using $CsF{\cdot}Al_2O_3$ as a reusable solid base catalyst was developed for both batch and continuous-flow systems, and Cs_3AlF_6 was identified as the active basic site for the addition reaction.



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Page No. – Page No.

Catalytic Stereoselective 1,4-Addition Reactions Using CsF on Alumina as Solid Base: A Heterogeneous Platform for Continuous-Flow Synthesis of Glutamic Acid Derivatives