A Catalyst-free Addition Reaction of Zinc Amide Enolates to *N*-Sulfonyl Imines

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For the introduction of amino functionality in complex organic molecules, nitrile and imine derivatives possessing a carbon-nitrogen multiple bond have been frequently utilized as good substrates.[1] When this type of reaction was conducted with metal enolates and imines, called the imino-Reformatsky reaction, 3-amino amide derivatives were efficiently obtained.[2] Due to the synthetic importance of 3-amino acid and their derivatives, this approach has been continuously considered and utilized as an efficient tool for the introduction of amino functionality in the 3-position of esters and amides.[3] To expand the scope of this strategy, recent studies are heavily focused on the asymmetrical approach of the imino-Reformatsky reaction. Regarding this subject, several attempts have been undertaken using various reaction systems as follows: diethylzinc,[4] diethylzinc/H_2O,[5] dimethylzinc/Ni(0),[6] Zn/sonication,[7] Zn/dibromoethane,[8] and diethylzinc/Rh(cat.).[9] In addition, application to a large scale production was also disclosed.[10] Despite the remarkable expansion of the imino-Reformatsky reaction, one interesting aspect is that, to the best of our knowledge, zinc enolates derived solely from α-halo esters have been mainly used in the recent progress. In contrast, a few limited examples have been reported concerning the application of zinc enolates derived from α-halo amide to the imino-Reformatsky reaction. In recent years, Rodriguez-Solla and co-workers reported the addition reaction of samarium enolates derived from both α-halo esters and amides to imines, resulting in the synthesis of β-amino esters or amides.[11] In their study, the presence of SmI_2 in either stoichiometric or catalytic amounts was very critical for completion of the reaction (Figure 1). Albeit the positive outcome of the work, it would be more attractive if the addition of zinc enolate to imine is carried out using a more versatile metal enolate without any additives including a metal-catalyst.

Considering both the simplicity of the reaction and our previous results utilizing highly active zinc metal,[12] we have decided to investigate the direct addition reaction of zinc enolates to *N*-tosyl imines in the absence of any additives. To our delight, the reactions proceeded very positively, yielding the expected products. Thus, we herein describe the results and suggest an alternative synthetic route for the preparation of 3-amino amide derivatives. The zinc enolates used in this study were easily prepared by the reaction of active zinc with readily available α-chloro acetamide.[12d] Also, the coupling partner *N*-tosyl imines were efficiently obtained through the literature protocol, which was a simple condensation procedure of *p*-toluenesulfonamide and sodium *p*-toluenesulfinate with the corresponding aldehydes in the presence of an acid catalyst at room temperature.[13]

In order to examine closely the feasibility of our strategy, a zinc enolate, 2-diethylamino-2-oxoethylzinc chloride (**A**), derived from the reaction of highly active zinc (Zn*) with α-chloro-*N*,*N*-diethyl acetamide, was first reacted with *N*-benzylidene-4-methylbenzenesulfonamide in THF at refluxing temperature in the absence of any additives. The addition reaction was monitored by gas chromatography (GC) and/or thin layer chromatography (TLC). The reaction took place smoothly at room temperature to produce a coupling product. A more efficient conversion to the coupling product was achieved by a simple change of reaction temperature to reflux. After being stirred at a refluxing temperature for 1 h, an appropriate workup procedure was executed to afford the product, *N*,*N*-diethyl-3-(4-methylphenylsulfonamido)-3-phenylpropanamide (**1a**), in 85% isolated yield (entry 1, Table 1). More results are summarized in Table 1. Diverse coupling reactions of **A** with *N*-(tosylaryl) imines functionalized with Br, CN, Cl, and NO_2 were

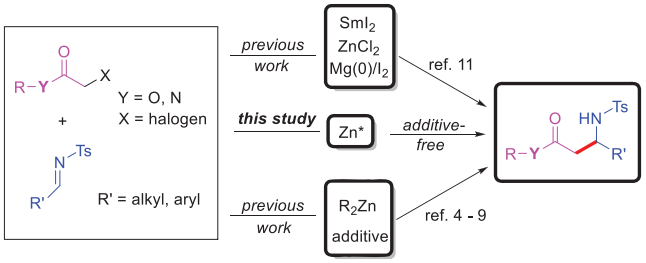

Figure 1. Schematic diagram of the addition reactions of zinc enolates to imines.

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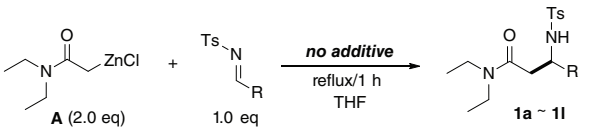
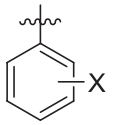
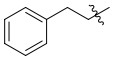
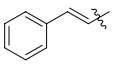
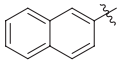
Table 1. Addition reaction of **A** with *N*-tosyl imines.



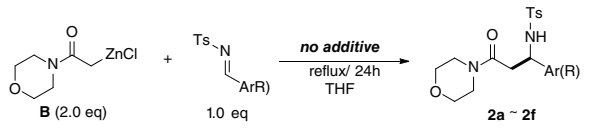
Entry	Imine		Product	Yield[a]
1		X = H	**1a**	85
2		X = 3-Br	**1b**	70
3		X = 4-CN	**1c**	80
4		X = 4-Cl	**1d**	98
5		X = NO_2	**1e**	58
6		*n* = 3	**1f**	69
7			**1g**	62
8			**1h**	65
9			**1i**	61
10			**1j**	57
11			**1k**	52
12			**1l**	77

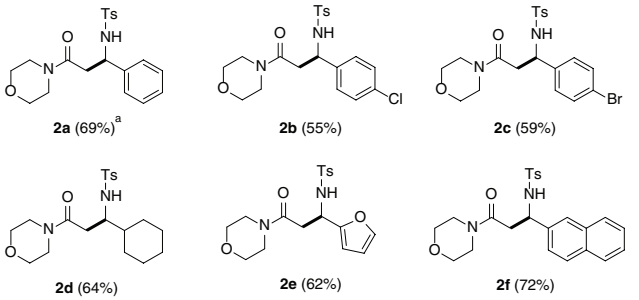
[a] Isolated yield (based on imine).

also conducted effectively to furnish the corresponding amides (**1b–1e**) in good to excellent yields (entries 2–5, Table 1), except in the case of NO_2, which had marginally lower yield. Under the same conditions, *N*-(tosylalkyl) imines were also appropriate substrates to couple with **A**, giving rise to amide derivatives (**1f–1g**) in relatively low yields (entries 6 and 7, Table 1). Imine containing a hetero aryl moiety was also a suitable substrate in our system (entries 8 and 9, Table 1), providing **1h** and **1i** in 65 and 61% yields, respectively. Extended efforts were demonstrated with more imines including a fused ring (entries 10–12, Table 1) furnishing the corresponding amides **1j**, **1k**, and **1l**.

To explore the scope of the reaction, further experiments were conducted with 2-morpholino-2-oxoethylzinc chloride (**B**), which was easily prepared using readily available 4-chloroacetylmorpholine and highly active zinc. Once again, all of the coupling reactions were carried out in the absence of any additional additives and progressed well at refluxing temperature in THF to provide the anticipated products in the range of moderate to good isolated yields. For the completion of the coupling, an extended reaction time was required. The results are summarized in Table 2. Treatment of zinc enolate **B** with *N*-(tosylaryl) imines

Table 2. Addition reaction of **B** with *N*-tosylimines.





[a] Isolated yield (based on imine).

resulted in the formation of the desired products (**2a**, **2b**, and **2c**, Table 2) after reacting for 24 h at reflux. Not only alkyl but also heteroaromatic *N*-tosyl imine was successfully coupled with **B** to give *N*-tosylamino amides (**2d** and **2e**, Table 2) in 64 and 62% isolated yields, respectively. Imine containing a bulky substrate also underwent the above reaction, affording **2f** in 72% isolated yield.

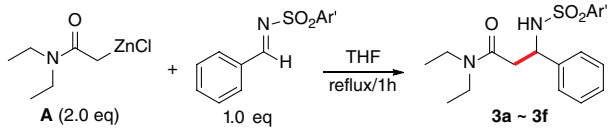
Not only zinc enolates but also sulfonyl imines were diversified using nitro aryl sulfonyl imines as well as hetero aryl sulfonyl imines. Coupling reactions of **A** with various sulfonyl imines were performed at the conditions used previously in our study, resulting in the formation of amides (**3a–3f**) with moderate yields. The results are summarized in Table 3.

Encouraged by the successful applications of **A** and **B**, we tested a somewhat different type of enolate, the zinc ester enolate (**C**), which was prepared using active zinc and *t*-butyl chloroacetate. Zinc ester enolate was subjected to a reaction with various aryl and alkyl *N*-tosyl imines under the same conditions as above (no additives, refluxing temperature in THF). Unfortunately, we found that the expected coupling product was not obtained. Instead, the starting material imine and several minor products were identified even at elevated reaction temperatures.

Taking into account the fact that free amine functionality can be readily obtained from *N*-tosyl amines using a simple manipulation,[14] **1a** was treated with lithium naphthalenide. The β-amino amide (**1aa**) was obtained in 40% yield (Scheme 1).

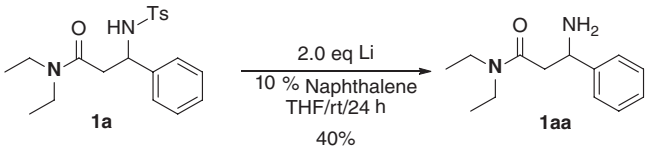
In conclusion, we established a potential synthetic protocol for the preparation of β-amino amides. This work was accomplished by the direct addition of zinc amide enolates to *N*-sulfonyl imines in the absence of any metal-catalyst under mild conditions.[15] Due to the operational simplicity of the proposed method, it can be further utilized in synthetic organic chemistry. Further studies to elucidate the scope of this approach are currently underway in our laboratory.

Table 3. Addition reaction of **A** with various *N*-sulfonyl imines.



Entry	Ar'	Product	Yield (%)[a]
1	*p*-$NO_2C_6H_4$	**3a**	55
2	*o*-$NO_2C_6H_4$	**3b**	50
3	2-thienyl	**3c**	61
4	8-quinolyl	**3d**	49
5	2-pyridyl	**3e**	58
6	3-pyridyl	**3f**	51

[a] Isolated yield (based on imine).



Scheme 1 Preparation of β-amino amide.

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Supporting Information. Additional supporting information is available in the online version of this article.

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15. Representative addition reaction with an imine; preparation of *N*,*N*-diethyl-3-(4-methylphenylsulfonamido)-3-(4-chlorophenyl)propanamide (1d); Into a 25 mL round-bottomed flask was added 4.0 mL of 2-(diethylamino)-2-oxoethylzinc chloride (0.5 M in THF, 2.0 mmol) under an argon atmosphere. Next, *N*-(4-chlorobenzylidene)-4-methylbenzenesulfonamide (0.31 g, 1.0 mmol) dissolved in 2.0 mL of THF was slowly added via a syringe while being stirred. The resulting mixture was refluxed for 1 h, then cooled down to room temperature. The reaction mixture was quenched with 3 M NH_4Cl solution, and then extracted with ethyl ether (10 mL ×3). The combined organic layers were washed with saturated $NaHCO_3$ (*aq*), $Na_2S_2O_3$ (*aq*) solution and brine, and then dried over anhydrous Na_2SO_4. Concentrated *in vacuo* to yield a crude solid product. Recrystallization from ethyl ether afforded 0.40g of **1d** in 98% isolated yield as a white solid. Mp = 134–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.0 Hz, 3H), 2.38 (s, 3H), 2.62 (dd, *J* = 15.5, 5.0 Hz, 1H), 2.73 (dd, *J* = 15.5, 5.0 Hz, 1H), 3.03 (dq, *J* = 7.5, 3.0 Hz, 2H), 3.17–3.32 (m, 2H), 4.64 (dd, *J* = 11.0, 5.0 Hz, 1H), 7.06–7.09 (m, 3H), 7.11–7.16 (m, 4H), 7.57 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 143.1, 138.6, 137.6, 133.2, 129.3, 128.4, 128.2, 127.1, 54.5, 42.2, 40.4, 38.2, 21.5, 14.1, 12.9; HRMS Calcd for $C_{20}H_{25}ClN_2O_3S$: 408.1274; Found: 408.1279.

