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Sulfonylimidates as Nucleophiles in Catalytic Addition Reactions

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Recently, catalytic direct-type addition reactions of carbonyl compounds have been developed extensively.[1] The majority of those reported reactions can be classified into two groups: enamine formation pathway[2] and enolate formation mechanism. In the former case, primary or secondary amines have been employed to form in situ enamines, which are more nucleophilic than the parent carbonyl compounds. In the latter case, both metal and nonmetal catalysts (usually tertiary amines) have been used to generate reactive enolates in situ. Although metals have been shown to catalyze the reactions of α-alkyl-substituted carbonyl compounds with the assistance of the Lewis acidity of the metal,[3] most of the reactions are limited to the carbonyl compounds bearing electron-withdrawing groups such as C═O, NO_2, CN, and OH at α-positions. To the best of our knowledge, there are no reports of simple tertiary amine-catalyzed direct-type addition reactions of carbonyl compounds bearing no activating functional groups at α-positions. Since tertiary amines are usually easy to handle, stable, and offer tunability, our interest was directed to the realization of this attractive reaction.

Direct-type reactions of nonactivated carbonyl compounds are notoriously difficult due to the relatively high pK_a values of the α-protons. Imines offer an additional possibility to tune reactivity, that is, the substituent on the nitrogen atom, which may allow us to control their reactivity. In order to lower the pK_a value of α-positions, sulfonyl-substituted imine **2** was selected for the preliminary investigation (Scheme 1). The adduct **3** was obtained in the presence of 10 mol % of Et_3N along with formation of the more stable enesulfonamide tautomer **4**. Acidic workup converted both adducts to keto product **5** (37% yield), but a considerable amount of chalcone (23% yield) was obtained as a result of carbamate elimination.

This result prompted us to investigate sulfonylimidates[4] as they were expected not to readily tautomerize to the corresponding enesulfonamides due to the stabilizing effect of the neighboring oxygen atoms, although the pK_a value of sulfonylimidate can be expected to be higher than that of the corresponding sulfonylimine. To our delight, the reaction of sulfonylimidate **6a** (R^3 = Me, R^4 = Me, R^5 = Ph) with imine **1a** proceeded smoothly in the presence of a catalytic amount of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to afford the adduct **7a** in good yield (Table 1, entry 3), while no products were obtained in the absence of base or with weaker base, Et_3N (Table 1, entries 1 and 2). The reaction conditions were optimized in order to improve selectivity, and a high diastereoselectivity was observed under the conditions in Table 1, entry 9. Namely, sulfonylimidate **6c** (R^3 = *i*Pr, R^4 = Me, R^5 = 2,5-xylyl) was reacted with imine **1b** (R^1 = Ph, R^2 = Boc) in the presence of DBU (5 mol %) in DMF at 0 °C to afford the desired adduct in excellent yield and diastereoselectivity (95% yield, *anti*/*syn* = 96/4).[5] Enesulfonamide tautomers were not observed in any case. This is the first example of a tertiary amine-catalyzed direct-type reaction of α-alkyl-substituted ester equivalents and the first use of sulfonylimidates in a catalytic direct-type reaction.

Scheme 1. Direct-Type Reaction of Sulfonylimine **2** with Imine **1a** (R^1 = Ph, R^2 = CO_2Et)

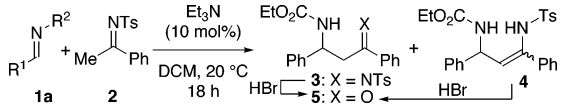
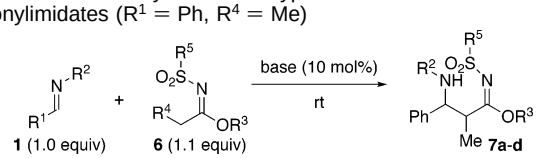


Table 1. Base-Catalyzed Direct-Type Reactions of Sulfonylimidates (R^1 = Ph, R^4 = Me)



entry	R^2	R^3	R^5	base	solvent	yield (%)	*anti*/*syn*[a]	product
1	CO_2Et	Me	Ph	−	DCM	0	−	−
2	CO_2Et	Me	Ph	Et_3N	DCM	0	−	−
3	CO_2Et	Me	Ph	DBU	DCM	90	69/31	**7a**
4	CO_2Et	Me	Ph	DBU	DMF	quant	62/38	**7a**
5	CO_2Et	*i*Pr	Ph	DBU	DMF	80	79/21	**7b**
6	Boc	*i*Pr	Ph	DBU	DMF	72	93/7	**7c**
7	Boc	*i*Pr	2,5-xylyl	DBU	DMF	65	95/5	**7d**
8[b]	Boc	*i*Pr	2,5-xylyl	DBU	DMF	75	96/4	**7d**
9[b,c]	Boc	*i*Pr	2,5-xylyl	DBU	DMF	95	96/4	**7d**

[a] Determined by ^{1}H NMR spectroscopy of crude products. [b] 0 °C. [c] 1.5 equiv of **1** and 1.0 equiv of **6** used. Catalyst loading was 5 mol %.

The optimized conditions were found to be applicable to a wide range of substrates as summarized in Table 2. Et-substituted and nonsubstituted products **7e** and **7f** could also be obtained in good yields (Table 2, entries 2 and 3), although an excess amount of **6e** (R^3 = Et, R^4 = H, R^5 = Ph) was necessary in order to suppress overreaction.[6] Tosyl (Ts) imine was also found to be a good substrate, affording the product with high selectivity (Table 2, entry 4). Boc imines derived from aromatic aldehydes bearing electron-donating and -withdrawing substituents, *ortho*-, *meta*-, and *para*-substituted benzaldehydes, as well as heteroaromatic aldehydes provided the desired adducts in high yields with high diastereoselectivity (Table 2, entries 5−12). It is notable that nonaromatic aldehyde-derived imines gave the desired products in moderate to high yields and diastereoselectivities (Table 2, entries 13−20). Iminoester **1r** (R^1 = EtO_2C, R^2 = 4-$MeOC_6H_4$) reacted successfully with sulfonylimidate **6c**, providing α-amino acid precursor **7x** (Table 2, entry 21). Notably, mixing benzaldehyde (1.5 equiv), 2,5-xylylsulfonamide (1.5 equiv), and sulfonylimidate **6c** (1 equiv) with DBU (10 mol %) and 4 Å molecular sieves (MS 4A) furnished the desired adduct in good yield (70%) with excellent diastereoselectivity (*anti*/*syn* = 95/5).[7]

Sulfonylimidate **6a** also reacted with methyl acrylate in a Michael-like reaction, leading to the sulfonylimidate **8**. Furthermore,

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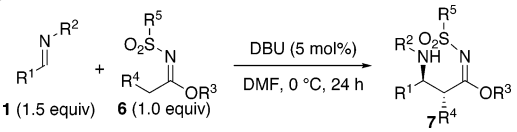
Table 2. DBU-Catalyzed Direct-Type Reactions of Sulfonylimidates

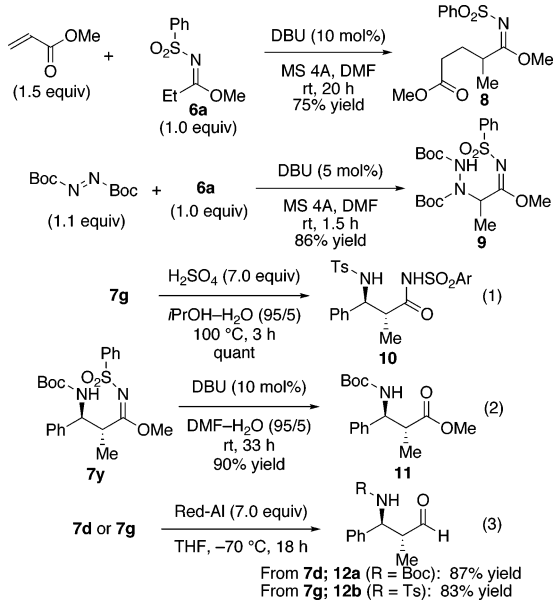


1 (1.5 equiv) **6** (1.0 equiv) **7**

entry	R^1	R^2	R^3	R^4	R^5	yield (%)	*anti*/*syn*[a]	**7**
1	Ph	Boc	*i*Pr	Me	2,5-xylyl	95	96/4	**7d**
2	Ph	Boc	*i*Pr	Et	2,5-xylyl	94	97/3	**7e**
3[b,c,d]	Ph	EtO_2C	Et	H	Ph	79	—	**7f**
4[c]	Ph	Ts	*i*Pr	Me	2,5-xylyl	91	96/4	**7g**
5[e]	*p*-$MeOC_6H_4$	Boc	*i*Pr	Me	2,5-xylyl	91	95/5	**7h**
6	*p*-FC_6H_4	Boc	*i*Pr	Me	2,5-xylyl	87	97/3	**7i**
7	*m*-MeC_6H_4	Boc	*i*Pr	Me	2,5-xylyl	quant	97/3	**7j**
8[e]	*o*-MeC_6H_4	Boc	*i*Pr	Me	2,5-xylyl	64	93/7	**7k**
9	*m*-vinyl-C_6H_4	Boc	*i*Pr	Me	2,5-xylyl	97	97/3	**7l**
10	2-furyl	Boc	*i*Pr	Me	2,5-xylyl	92	95/5	**7m**
11	2-thienyl	Boc	*i*Pr	Me	2,5-xylyl	90	98/2	**7n**
12	2-pyridyl	Boc	*i*Pr	Me	2,5-xylyl	91	98/2	**7o**
13[c]	PhCH=CH	Ts	*i*Pr	Me	2,5-xylyl	80	98/2	**7p**
14[c]	cyclopropyl	Ts	*i*Pr	Me	2,5-xylyl	84	87/13	**7q**
15[c,d]	cyclopropyl	Boc[h]	*i*Pr	Me	2,5-xylyl	quant	88/12	**7r**
16[c,d,g]	*c*-C_6H_{11}	Ts[h]	Me	Me	*p*-MeC_6H_4	51	83/17	**7s**
17[c,d,g]	*c*-C_6H_{11}	Ts[h]	*i*Pr	Me	*p*-MeC_6H_4	59	84/16	**7t**
18[c,d,g]	*i*Pr	Ts[h]	Me	Me	*p*-MeC_6H_4	56	69/31	**7u**
19[c,d,g]	*i*Pr	Ts[h]	*i*Pr	Me	*p*-MeC_6H_4	54	87/13	**7v**
20[c,f]	*t*Bu	Ts	Me	Me	*p*-MeC_6H_4	51	14/86	**7w**
21[c,d]	EtO_2C	*p*-$MeOC_6H_4$	*i*Pr	Me	2,5-xylyl	80	55/45[i]	**7x**

[a] Determined by ^{1}H NMR spectroscopy of the crude product or isolated product. [b] 5 equiv of **6** and 1 equiv of **1** were used. [c] MS 4A (167 g/mol) were added. [d] 10 mol % of DBU was used. [e] 38 h. [f] 40 °C, 36 h. [g] Room temperature. [h] 3 equiv of **1** was used. [i] Major/minor.

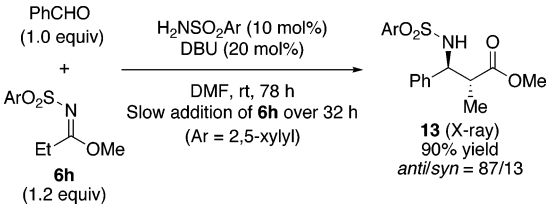
Scheme 2. DBU-Catalyzed Direct-Type Reactions of Sulfonylimidate **6a**



the reaction of **6a** with an azodicarboxylate could be catalyzed efficiently by 5 mol % of DBU to give the adduct **9** in high yield (Scheme 2).

Several transformations of the obtained sulfonylimidates are shown in eqs 1−3. Since sulfonylimidates were rather resistant to acid, relatively harsh conditions were needed for hydrolysis of **7g** (eq 1). The hydrolysis product was not the expected ester but the *N*-sulfonyl amide **10**. On the other hand, mild basic conditions (a catalytic amount of DBU) hydrolyzed sulfonylimidate **7y** to the corresponding ester **11** in excellent yield (eq 2). Reduction of **7d** or **7g** with Red-Al gave aldehyde **12a** or **12b**,[8] respectively (eq 3), which could be used for further transformations.

Scheme 3. Direct Formation of β-Amino Acid Ester from Aldehyde and Sulfonylimidate



With the knowledge that sulfonylimidates are hydrolyzed with the assistance of catalytic DBU, direct formation of β-amino acid ester from an aldehyde and sulfonylimidate could be realized (Scheme 3). Ester **13**, which is a biologically important β-amino acid derivative,[9] was obtained in high yield with good selectivity.[10]

In summary, we have shown the first example of highly selective catalytic direct-type addition reactions of sulfonylimidates. A tertiary amine, DBU, is a good catalyst in Mannich-type, Michael-type, and azodicarboxylate addition reactions. In Mannich-type reactions, high *anti*-selectivity was observed. Direct formation of β-amino acid derivatives from aldehydes and sulfonylimidates could be also achieved. Further applications of sulfonylimidates as well as the development of asymmetric variants are currently being investigated.

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Supporting Information Available: X-ray diffraction analyses, experimental procedures, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The relative configuration of the product was determined by X-ray diffraction analysis. Details of X-ray crystal structures of several sulfonylimidates and the rational explanation for high *anti*-selectivity are documented in Supporting Information.

(6) Excess starting material **6e** could be recovered (403%) by chromatography.

(7) See Supporting Information for details.

(8) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc.* **2004**, *126*, 15652. In their report, sulfinylamidine was reduced to sulfinylaldimine by Red-Al. In our case, the corresponding sulfonylaldimine was not observed after workup, but the aldehyde was obtained directly.

(9) Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792 and the references cited therein.

(10) The proposed mechanism is demonstrated in Supporting Information.

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