Homogeneous Catalysis

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Addition Reactions of Sulfonylimidates with Imines Catalyzed by Alkaline Earth Metals**

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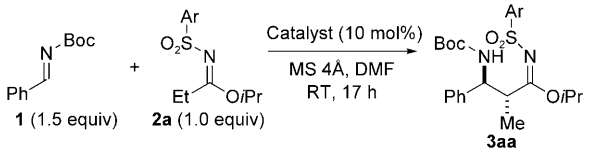
The role of alkaline earth metals as catalysts in organic chemistry has received relatively little attention from the academic community in recent years. Despite the attractive features of these metals, which are vastly abundant, inexpensive, and commercially available and which have no obvious toxicity associated with them, only sporadic reports have appeared in the literature.[1] Alkaline-earth-metal alkoxides display duel properties with both Lewis acidic and Brønsted basic character, which makes them very attractive in the direct addition of enolates to electrophiles.[2] Ongoing research in our group seeks to utilize these properties for the promotion of efficient organic transformations. We have demonstrated the abilities of calcium and strontium alkoxides in catalytic asymmetric Michael reactions[3] and 1,4-additions of glycine derivatives.[4]

Recently our group also reported the first example of sulfonylimidates acting as nucleophiles in catalytic addition reactions with imines.[5] While most of the reports on direct addition reactions of esters with imines had been limited to ester substrates bearing electron-withdrawing groups at the α-position,[6,7] sulfonylimidates with alkyl groups at the α-position reacted with imines smoothly in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), affording the adducts in good yields with high *anti* selectivity.

Herein we report the role of alkaline-earth-metal alkoxides in direct additions of sulfonylimidates to imines with controllable diastereoselectivities. With $Mg(OtBu)_2$ in DMF, *anti* product could be obtained, while using $[\{Sr(hmds)_2\}_2]$[8] (hmds = hexamethyldisilazide) in THF afforded *syn* products. A rationale for the dependence of the diasteroselectivity on the reaction conditions is also described.

Initial screening of alkaline-earth-metal alkoxides revealed that $Mg(OtBu)_2$ was the most efficient for the promotion of our test reaction (Table 1, entry 4), offering high yield and *anti* selectivity (Table 1). The same level of *anti* selectivity as observed in the previously reported DBU-catalyzed reactions could be ascribed to the formation of the naked enamide anion, which is perhaps facilitated by the relatively polar solvent DMF (see below). Considering possible asymmetric variants of this reaction, we surmised that a metal bearing a chiral ligand, for example, should be as close to the enamide anion as possible. We thus examined less polar solvents to lessen metal–countercation dissociation.

Table 1: Screening of metal bases for *anti*-selective addition reactions. The best result is shown in bold.[a]



Entry	Catalyst	Yield [%]	*anti*/*syn*[b]
1	$Ca(OiPr)_2$	72	93:7
2	$Sr(OiPr)_2$	75	93:7
3	$Ba(OiPr)_2$	68	90:10
4	$Mg(OtBu)_2$	**94**	**96:4**
5	$Ca(OtBu)_2$	78	87:13
6	$Sr(OtBu)_2$	61	80:20
7	$Ba(OtBu)_2$	80	90:10
8[c]	$Mg(OtBu)_2$	>99	94:6

[a] Ar = 2,5-xylyl for entries 1–7. Boc = *tert*-butoxycarbonyl. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] Ar = *p*-NO_2-C_6H_4.

However, the reactions of **2a** in less polar solvents such as CH_2Cl_2 and toluene failed to proceed or gave low yields owing to the low efficiency of the deprotonation. To our delight, by placing an electron-withdrawing group on the aryl functionality (**2b**), less polar solvents could be used. The surprising aspect was that *syn* selectivity in the product was obtained instead of *anti* products. Using $Ca(OiPr)_2$ or $Ba(OiPr)_2$ the products could be obtained in moderate yields and good *syn* selectivity of close to 9:1 (Table 2, entries 1 and 3). Stronger amide bases such as $[\{Sr(hmds)_2\}_2]$ were more active and afforded the product in 98% yield after 18 h (Table 2, entry 4). The addition of ligand **4** generally increased the *syn* selectivity (Table 2, entries 1–4 vs. entries 5–8). Higher diastereoselectivity of 94:6 could be obtained at 0°C, but there was no advantage in lowering the temperature even further (Table 2, entries 9 and 10). To elucidate the origin of the observed *syn* selectivity, the reaction of sulfonylimidate **2b** in THF using DBU as a catalyst was conducted (Table 2, entry 11), leading to the *anti* products. This result and the result obtained in Table 1, entry 8 reveal that both a metal catalyst and a less polar solvent system are crucial for *syn*-selective reactions and that the influence of the sulfonyl group on the diastereoselectivity is small although the *p*-NO_2

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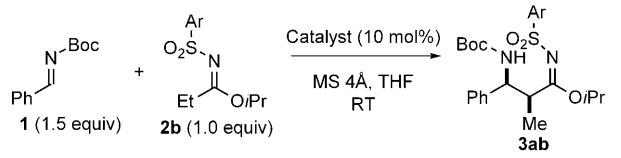
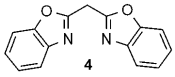
Table 2: Optimization for *syn*-selective addition reactions. The best result is shown in bold.[a]



Entry	Catalyst	*t* [h]	Yield [%]	*anti*/*syn*[b]
1	$Ca(OiPr)_2$	48	56	11:89
2	$Sr(OiPr)_2$	48	34	32:68
3	$Ba(OiPr)_2$	48	55	15:85
4	$1/2[\{Sr(hmds)_2\}_2]$	18	>99	14:86
5[c]	$Ca(OiPr)_2$	48	68	11:89
6[c]	$Sr(OiPr)_2$	48	45	7:93
7[c]	$Ba(OiPr)_2$	48	65	9:91
8[c]	$1/2[\{Sr(hmds)_2\}_2]$	24	**92**	**7:93**
9[c,d]	$1/2[\{Sr(hmds)_2\}_2]$	48	76	6:94
10[c,e]	$1/2[\{Sr(hmds)_2\}_2]$	72	65	6:94
11	DBU	24	77	74:26

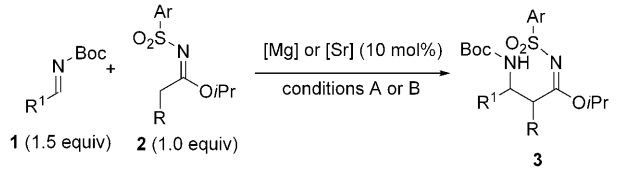
[a] Ar = *p*-NO_2-C_6H_4. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Ligand **4** was used. [d] At 0 °C. [e] At −20 °C.



substituent is required for the reaction to proceed in a less polar solvent.

With these two systems in hand, we explored the scope of the catalytic reaction (Table 3). High *anti* selectivity was observed when conditions A ($Mg(OtBu)_2$, DMF, Ar = 2,5-xylyl) were used, while high yields of *syn*-selective products were obtained under conditions B ($[\{Sr(hmds)_2\}_2]$, ligand **4**, THF, Ar = *p*-NO_2-C_6H_4). Notably, heteroaromatic (Table 3, entries 7–9) and aliphatic (Table 3, entries 11, 13) as well as aromatic Boc imines (Table 3, entries 1–6) all gave adducts with high selectivities. Interestingly, in contrast to the *syn* selectivity observed under conditions set B with the *N*-Boc imine (Table 3, entry 1), the corresponding *N*-Ts imine (Ts = toluene-4-sulfonyl) provided *anti* selectivity under both sets of conditions A and B (Table 3, entry 10).

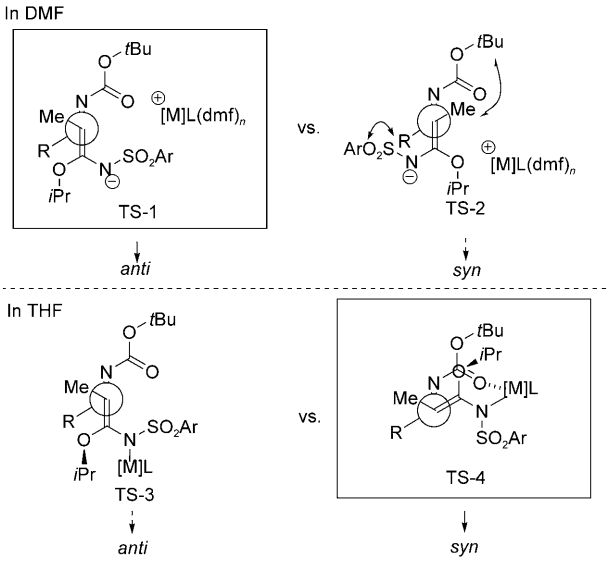
Table 3: Substrate scope of addition reactions of sulfonylimidates (R = Me).



		$Mg(OtBu)_2$ Conditions A[a]		$[\{Sr(hmds)_2\}_2]$ Conditions B[a]	
Entry	R^1	Yield [%]	*anti*/*syn*[b]	Yield [%]	*anti*/*syn*[b]
1	Ph	94 (**3aa**)	96:4	98 (**3ab**)	7:93
2	*p*-$MeOC_6H_4$	92 (**3ba**)	95:5	99 (**3bb**)	5:95
3	*p*-FC_6H_4	>99 (**3ca**)	98:2	87 (**3cb**)	8:92
4	*m*-MeC_6H_4	>99 (**3da**)	96:4	99 (**3db**)	6:94
5	*o*-MeC_6H_4	93 (**3ea**)	93:7	99 (**3eb**)	11:89
6	*m*-vinyl-C_6H_4	>99 (**3fa**)	96:4	90 (**3fb**)	7:93
7	2-furyl	90 (**3ga**)	96:4	95 (**3gb**)	6:94
8	2-thienyl	96 (**3ha**)	98:2	99 (**3hb**)	7:93
9	2-pyridyl	95 (**3ia**)	97:3	70 (**3ib**)	6:94
10[c]	Ph	98 (**3ja**)	67:33	94 (**3jb**)	93:7
11	cyclopropyl	94 (**3ka**)	85:15	99 (**3kb**)	15:85
12[d]	Ph	80 (**3la**)	95:5	85 (**3lb**)	5:95
13[e]	cyclohexyl	99 (**3ma**)[c]	80:20[c]	82 (**3mb**)	16:84

[a] Conditions A: DMF, RT, 17 h, Ar = 2,5-xylyl. Conditions B: Ligand **4** (11 mol%), THF, RT, 24 h, Ar = *p*-NO_2-C_6H_4. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Ts imine instead of Boc imine was used. [d] R = Et. [e] 2 equiv imine used.

Proposed transition-state models to explain both *syn* and *anti* selectivity are depicted in Scheme 1. As reported,[5] we assume the kinetically favorable formation of the *Z*-enamide



Scheme 1. Proposed transition-state models. (L = ligand).

anion. In DMF the metal cation/enamide anion ion pair is thought to be preferred over covalent bond formation between the two units, owing to solvation of the metal cation, which results in an *anti*-selective transition state similar to that observed when DBU is used (TS-1). In contrast, in less polar solvent (THF), a neutral metal enamide species is thought to predominate. TS-3, which is almost identical to TS-1, is still possible, but the bulky metal moiety prevents the *i*Pr group from being placed in the olefin plane, leading to a decrease in enamide nucleophilicity. On the other hand, TS-4, in which the metal activates the imine by coordination to the Boc carbonyl oxygen atom, may become more favorable, resulting in the *syn*-selective formation of products. The corresponding chelation model affording *anti* product is less likely because of the significant steric repulsion between the aryl sulfonyl group and the Boc group (not shown). The *anti* selectivity observed in the case of *N*-sulfonyl-protected imine is probably due to the poor coordinating ability of the sulfonyl group.

Relative configurations of the products were unequivocally assigned by X-ray diffraction analyses (Figure 1).[9] It is notable that an intramolecular hydrogen bonding interaction between a proton of BocN–H and one of the sulfonyl oxygen atoms is suggested only in the *anti* situation. This observation does not contradict the fact that N–H chemical shifts in the ^{1}H NMR spectra of *anti* products are all more deshielded than those of *syn* products by 0.2–0.5 ppm.

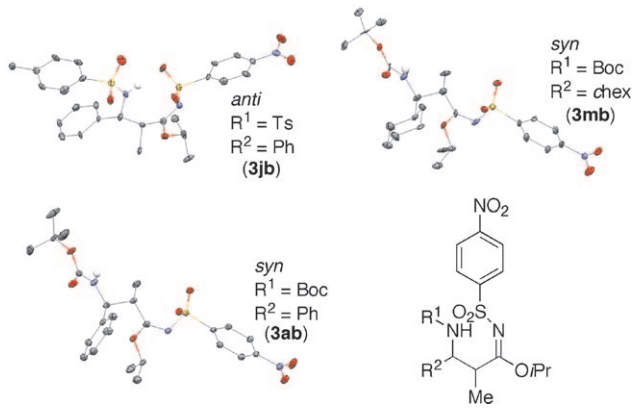
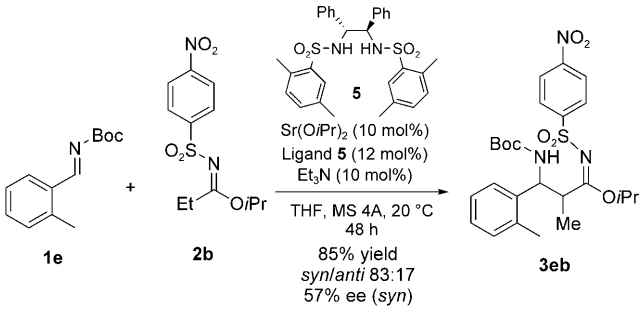


Figure 1. X-ray crystal structures of the products. *c*hex = cyclohexyl. S yellow, O red, N blue, C gray, H white.

A preliminary result of a catalytic asymmetric variant is shown in Scheme 2.[10] Although the enantioselectivity is moderate, this is the first example of a catalytic asymmetric Mannich-type reaction of a sulfonylimidate.[11,12]



Scheme 2. Catalytic asymmetric addition reaction of sulfonylimidate with *N*-Boc imine.

In summary, addition reactions of sulfonylimidates to imines have been successfully catalyzed by alkaline-earth-metal alkoxide salts, which are abundant, inexpensive, and nontoxic. Diastereoselectivity is highly dependent on solvents and catalysts; the reactions in DMF proceed with *anti* selectivity no matter whether DBU or metal alkoxide is used as catalyst, while in THF *syn*-selective products are obtained using a metal alkoxide. Substrate scope is broad, and aromatic, heteroaromatic, as well as cyclic and acyclic aliphatic imines can be used, affording the *syn* or *anti* products selectively by utilizing two different sets of conditions. Rational transition-state models to explain both *syn* and *anti* selectivity of each set of conditions are proposed. The first example of a catalytic asymmetric addition reaction of a sulfonylimidate with an imine has also been demonstrated. Further optimization of the asymmetric variant as well as application to other electrophiles are currently ongoing.

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