Alkaline Earth Metal Catalysis

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Direct Michael, Aldol, and Mannich Additions Catalyzed by Alkaline Earth Metals

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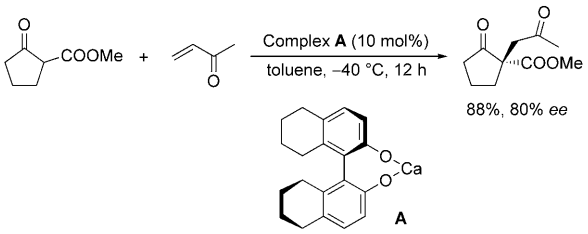
aldol reaction · alkaline earth metals · homogeneous catalysis · Mannich bases · Michael addition

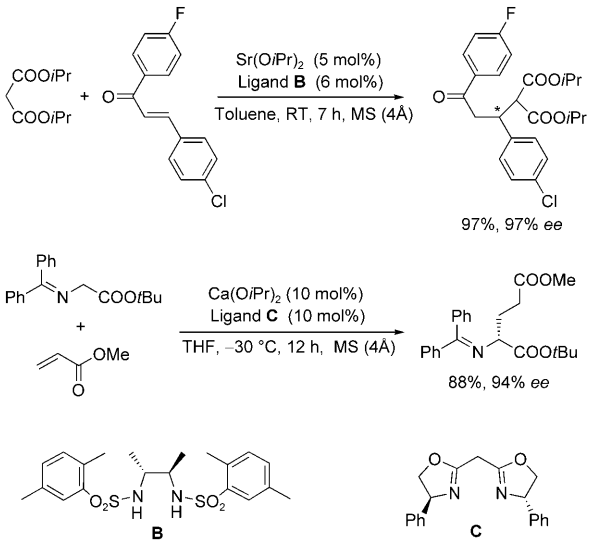
Alkaline earth metals are vastly abundant, inexpensive and commercially available, and also relatively nontoxic. Surprisingly, only a few examples of alkali earth metal catalyzed processes have been reported so far.[1] Evans and Nelson were the first, reporting an application of magnesium bisulfonamide complexes as catalysts for the enantioselective amination of *N*-acyloxazolidinones.[2] This approach provided an interesting stereoselective approach towards arylglycines.

Alkali earth metals show both Lewis acidic as well as Brønsted basic properties, which makes them ideal candidates as catalysts for enolate additions.[3] Kumaraswamy et al. reported on asymmetric Michael additions of various malonates and β-ketoesters to α,β-unsaturated ketones in the presence of binol–calcium complexes (Scheme 1; binol = 1,1′-2-binaphthol).[4] The best results were obtained with octahydrobinol complexes **A**.



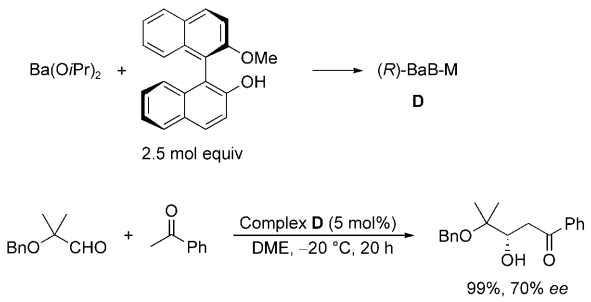
Scheme 1. Calcium-catalyzed asymmetric Michael additions according to Kumaraswamy et al.

Work from the Kobayashi group indicates that besides the binols also other bidentate ligands, such as Evans's bissulfonamides **B**[2] or bisoxazolines **C** can be used to control the stereochemical outcome of the reaction. While the sulfonamides give excellent results in strontium-catalyzed additions of malonates,[5] bisoxazolines are the ligands of choice for the addition of glycine imines (Scheme 2).[6] This allows the synthesis of highly functionalized amino acids.



Scheme 2. Alkaline earth metal catalyzed asymmetric Michael additions according to Kobayashi et al.

Shibasaki and Yamada figured out that besides lanthanoid complexes[3b] also chiral barium complexes are suitable catalysts for asymmetric aldol reactions.[7] Catalyst **D**, easily prepared from $Ba(OiPr)_2$ and binol methyl ether (Scheme 3), can be used for the direct addition of methyl ketones to various aldehydes (including those with α-H atoms!). It is assumed that both partners, the ketone enolate and the aldehyde, coordinate to the chiral modified barium complex. The best results are obtained in the presence of two



Scheme 3. Asymmetric barium-catalyzed aldol additions according to Shibasaki et al. Bn = benzyl, DME = 1,2-dimethoxyethane.

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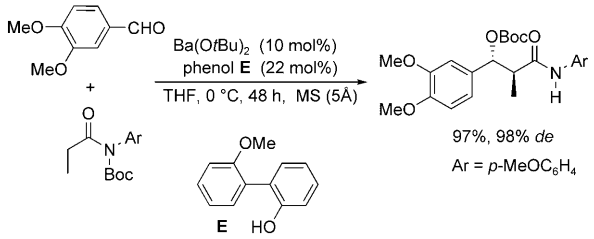
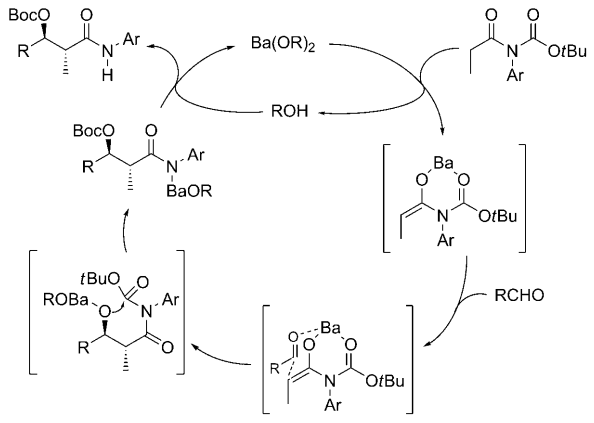
equivalents of the ligand (relative to Ba^{2+}), which indicates that probably two ligand molecules coordinate to the catalytically active barium ion in the transition state. Similar results are also obtained with calcium/hydrobenzoin complexes.[8]

The concept developed for ketones by Shibasaki et al. was further extended by Kobayashi et al. for derivatives of carboxylic acids. This is not a trivial issue, since the pK_a values of these derivatives are generally significantly higher than those of the related ketones. For this reason esters, for example, are not good candidates for direct aldol additions. This problem could be solved by using diacyl anilides.[9] Because of chelation, the second acyl group favors enolate formation. The best results were obtained with barium alkoxides, while rare earth metals are catalytically inactive. *ortho*-Substituted phenols **E** were found to be good proton sources. The aldol reaction works with aromatic as well as with aliphatic aldehydes (also with α-H toms!), but aromatic aldehydes generally give better yields (Scheme 4). The diastereoselectivities obtained are excellent, and the O-Boc-protected *anti* aldol products are formed preferentially. In principle, the stereochemical outcome of the reaction can be controlled by using chiral binol ligands, but so far the best selectivity has been only 33% *ee*.



Scheme 4. Barium-catalyzed direct aldol addition of amides. Boc = *tert*-butoxycarbonyl.

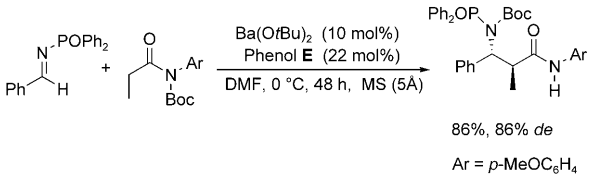
The reaction is thought to proceed via a chelated *E* enolate, which is formed in situ from the Boc-protected anilide and the barium alkoxide (Scheme 5). The aldehyde is activated by coordinating also to the chelated Ba^{2+} ion, and subsequent aldol addition via a chairlike transition state gives rise to the *anti* product. The barium alkoxide formed attacks



Scheme 5. Mechanism of the barium-catalyzed aldol addition.

the Boc protecting group, resulting in the formation of the protected aldol product.

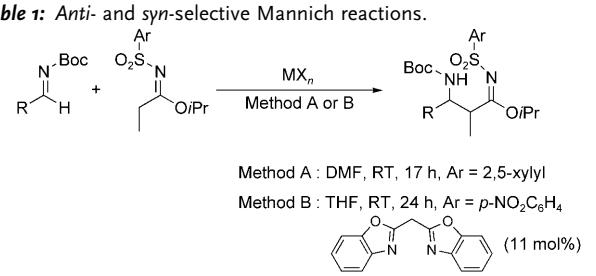
In principle, this protocol can also be extended to Mannich reactions, giving direct access to β-amino acids.[10] While no reaction is observed with N-alkylated imines, the imine reactivity can be significantly increased by the introduction of electron-withdrawing groups.[11] The best results are obtained with the corresponding *N*-diphenylphosphinoyl imines in DMSO or DMF. In analogy to the mechanism shown in Scheme 5, here, too, the *anti* product is formed preferentially and migration of the Boc group from the acyl- to the phosphinoyl-nitrogen atom is observed (Scheme 6).



Scheme 6. Barium-catalyzed Mannich additions of amides.

As an alternative to the *N*-Boc anilides, Kobayashi et al. presented the sulfonyl imidates very recently. These derivatives are also so acidic in the α-position that they can be deprotonated with catalytic amounts of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), but not with NEt_3.[12] While the hydrolysis of sulfonylimidates is also catalyzed by DBU, this approach allows the direct synthesis of N-protected β-amino acid derivatives in a straightforward one-pot protocol. Based on the relatively high acidity of the sulfonylimidates, alkoxides can be used as bases as well. Screening the different alkaline earth alkoxides indicated that the *anti* selectivities were good to excellent with all metals, while $Mg(OtBu)_2$ in DMF gave the best yields (Table 1, entry 1).[13] The results

Table 1: *Anti*- and *syn*-selective Mannich reactions.



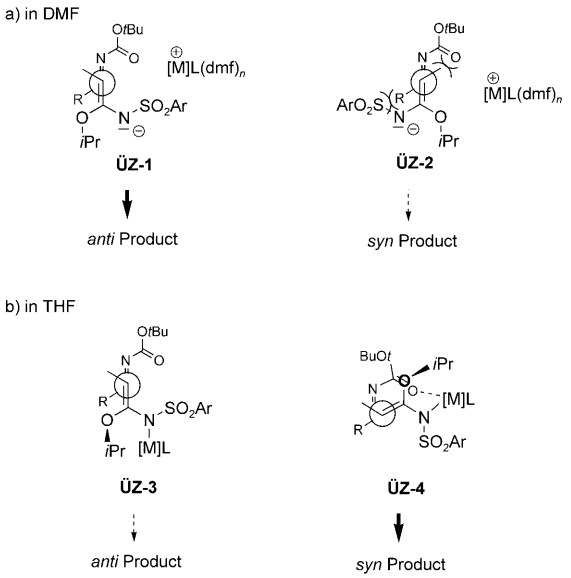
Entry	R	MX_n	Method	Yield [%]	*anti*/*syn*
1	Ph	$Mg(OtBu)_2$	A	94	96:4
2	Ph	$Ca(OiPr)_2$	B	68	11:89
3	Ph	$Sr(OiPr)_2$	B	45	7:93
4	Ph	$Ba(OiPr)_2$	B	65	9:91
5	Ph	$Sr(HMDS)_2$	B	92	7:93
6	*p*-$MeOC_6H_4$	$Mg(OtBu)_2$	A	92	95:5
7	*p*-$MeOC_6H_4$	$Sr(HMDS)_2$	B	99	5:95
8	2-furyl	$Mg(OtBu)_2$	A	90	96:4
9	2-furyl	$Sr(HMDS)_2$	B	95	6:94
10	2-thienyl	$Mg(OtBu)_2$	A	96	98:2
11	2-thienyl	$Sr(HMDS)_2$	B	99	7:93
12	cyclopropyl	$Mg(OtBu)_2$	A	94	85:15
13	cyclopropyl	$Sr(HMDS)_2$	B	99	15:85

obtained are comparable to those of the DBU-catalyzed reactions,[12] indicating that the reaction might proceed via a "naked" enamide anion. Its formation probably is favored by the polar solvent DMF.

As it should be possible in principle to control the absolute configuration of the Mannich products by using chiral ligands, such a "naked" anion is not really desired. Therefore, Kobayashi et al. investigated the Mannich reaction also in less polar solvents, in order to strengthen the interactions between the enolate and the metal counterion. Interestingly, in THF as a solvent, the *syn* product was formed preferentially, especially in the presence of an additional bisoxazoline ligand. Of all the alkoxides investigated so far, $Sr(OiPr)_2$ gave the best *syn* selectivity, although the yields were moderate (Table 1, entries 2–4).

This problem could be solved easily by switching to the more basic base $Sr(HMDS)_2$ (Table 1, entry 5; HMDS = hexamethyldisilazide). Based on these investigations, two different protocols are now available to synthesize either the *anti* or the *syn* product selectively. The *anti* Mannich product can be obtained by using 2,5-xylylsulfonyl imidates and $Mg(OtBu)_2$ in DMF (method A), while the *syn* products are formed from *p*-nitrophenylsulfonyl imidates in THF using $Sr(HMDS)_2$ as the base (method B).

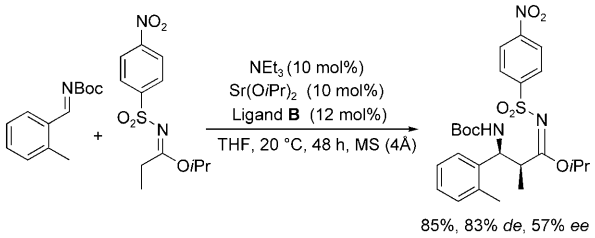
The different reaction behavior in the different solvents can be explained by the potential transition states involved in the coupling step (Scheme 7). In DMF as solvent the metal



Scheme 7. Mechanism of the barium-catalyzed Mannich addition. Details are given in the text.

ion is probably solvated, and the kinetically favored "naked" *Z*-enamide enolate can react with the imine via the sterically least hindered open transition state (**TS-1**) to give the *anti* product. The situation is different in THF. In this less polar solvent, a neutral metal enamide complex is most likely formed. Coordination of the Boc-protected imine at the metal ion can favor a cyclic transition state (**TS-4**), giving rise to the *syn* product.

In principle, an asymmetric version of this protocol is also possible, as illustrated by Mannich reactions carried out in the presence of the chiral bidentate bissulfonamide ligand **B**, which was used previously in Michael additions (Scheme 8).[5]



Scheme 8. Asymmetric strontium-catalyzed Mannich reactions.

There is still some room for improvement in the enantioselectivity, but this example nicely illustrates the potential of alkaline earth metal catalyzed reactions.

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