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Asymmetric Michael Additions of Homochiral Magnesium Amides

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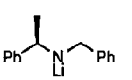
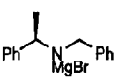
Abstract: The first asymmetric Michael addition of a homochiral magnesium amide is presented. Methylation of the resultant β-amino magnesium enolate was found to occur with excellent stereoselectivity, providing a direct strategy for the synthesis of homochiral *syn*-α-methyl-β-amino acids.

The propensity of lithium (*R*)-*N*-(α-methylbenzyl)benzylamide (*R*)-**1** to undergo highly diastereoselective Michael additions with α,β-unsaturated esters has been developed into a general protocol for the synthesis of homochiral β-amino acids.[1-5] Furthermore, the intermediate β-amino enolates have been shown to undergo asymmetric alkylation,[2] protonation,[2,3] and hydroxylation[4,5] reactions with generally excellent levels of control over the newly formed α-stereogenic centre.

Aside from the ubiquitous lithium amides, the nucleophilic properties of other metal amides have received only scant attention.[6,7] Although the basic properties of magnesium amides (R_2NMgBr) have attracted some interest,[8] their potential nucleophilicity has not been exploited. Herein we describe the first example of a highly diastereoselective Michael addition employing a homochiral *magnesium* amide.

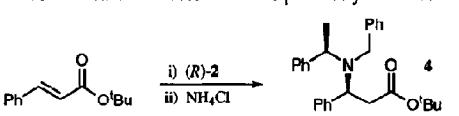


(*R*)-**1**



(*R*)-**2**

The preparation of the magnesium amide (*R*)-**2** was achieved by the addition of methylmagnesium bromide (4 eq.) to a THF solution (*ca.* 1M) of the parent homochiral amine (4.5 eq.) at room temperature. Generation of (*R*)-**2** was evidenced by the evolution of methane and, after stirring for 1 h, the resultant pale pink magnesium amide solution was cooled to -78°C. Upon addition of *tert*-butyl cinnamate **3** (1 eq.), the mixture was stirred at -78°C for 15h and then quenched with methanol. Subsequent analysis of the crude product by ^1H nmr spectroscopy (300MHz) indicated the generation of the known[2] β-amino ester **4** with excellent diastereoselectvity (≥95% d.e.) and in good conversion (90%). Interestingly, the sense of asymmetric induction in the Michael addition was thus identical to that observed in the previously described lithium amide variant.[2]

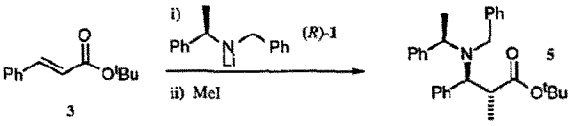


3

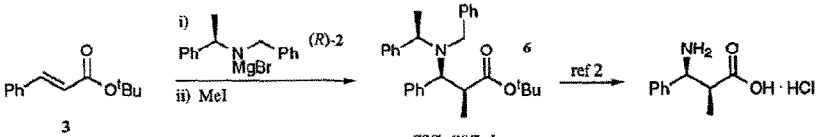
90%, ≥95% d.e.

It was next of interest to investigate whether the β-amino magnesium enolate resulting from the Michael addition of (*R*)-**2** to **3** could undergo stereoselective alkylation. We have previously communicated[2] that the analogous β-amino lithium enolate undergoes methylation with only moderate (30% d.e.) *anti* diastereoselectivity. In addition, it was discovered that an analogous reaction using (*E*)-*tert*-butyl 2-

methylcinnamate as the Michael acceptor, followed by diastereoselective enolate *protonation*, afforded the corresponding *syn* diastereoisomer **6** (*vide infra*) with excellent (>98% d.e.) stereocontrol.[2] It is noteworthy that both of these observations are consistent with preferential attack of the electrophile *anti* to the amino moiety, and this tendency has also been observed in the analogous enolate hydroxylation reactions.[4,5]



In marked contrast to the modest *anti* selectivity procured with the lithium amide (*R*)-**1**, the tandem addition-methylation reaction with *tert*-butyl cinnamate **3** using the homochiral magnesium amide (*R*)-**2** provided **6** in good yield (73%) and with excellent *syn* diastereoselectivity (19:1, 90% d.e.). As previously described,[2] such adducts can be readily deprotected to the free amino acids and consequently this procedure constitutes a direct approach to α-methyl-β-phenylalanine and derivatives thereof.



In conclusion, the first example of an asymmetric Michael addition using a homochiral magnesium amide has been reported. Although the sense of asymmetric induction in the Michael addition step was found to be the same with both the magnesium and lithium amides, the resultant β-amino enolates reacted in a stereodivergent manner with iodomethane. It consequently appears that the enolate π-face undergoing electrophilic attack in these reactions can be controlled by a simple change of counterion. The utility of homochiral magnesium amides in reactions using alternative enoate acceptors and electrophiles are currently under active investigation.

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